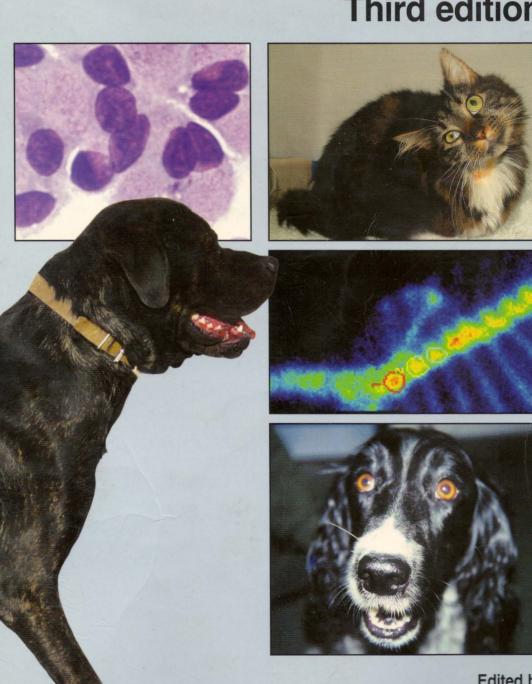


**Small Animal** Veterinary Saidings

**BSAVA Manual of** 

# **Canine and Feline** Neurology

Third edition



Edited by

Simon R. Platt and Natasha J. Olby

# BSAVA Manual of Canine and Feline Neurology

Third edition

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Manual of Canine & Feline Lameness Diagnosis

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## **Forewords**

The third edition of the BSAVA Manual of Canine and Feline Neurology has been expanded and revised to accommodate the advances made in this discipline since 1995 when the second edition was published. In common with all BSAVA manuals, this volume will form a ready source of practical information for practicing veterinary surgeons and veterinary students.

The layout of the book – in three main sections: diagnosis, neurological presentations and therapeutics – is practical and logical. The use of a standard 'problem-oriented' format for the chapters in the second part of the book will enable the practitioner quickly to obtain the relevant information he or she needs during the working day. However, the reader who is prepared to invest a little more time to read the book from cover to cover will find that it forms a definitive, authoritative and up-to-date guide to this complex and difficult area of veterinary medicine.

The authors and editors are recognized authorities in their respective fields and their expertise is apparent when reading the clear, concise chapters that they have produced. The BSAVA is grateful to the editors, Simon Platt and Natasha Olby, for their hard work and dedication in the preparation of this manual. We would also like to thank the authors. Without the enthusiasm and commitment of editors and authors, it would not be possible to produce BSAVA manuals.

Congratulations are due too, to the BSAVA Publications Committee and the team at BSAVA headquarters.

Ian Mason BVetMed PhD CertSAD DipECVD MRCVS BSAVA President 2004–2005

Fifteen years have passed since the publication of the first edition of this book, fifteen years that have seen mesmerising changes in the world of veterinary medicine.

The early days of specialization were largely restricted to those who practiced radiology and anaesthesia. Neurology was restricted in Europe to a few notable individuals in veterinary schools whose main interest may have been research but who applied their considerable intellects to the wellbeing of animal patients that came into their care. These selfless veterinarians also managed to instil enthusiasm and intrigue into many young clinicians who came under their influence. I was fortunate to be so influenced by two great clinicians in my early years, Ian Griffiths and Leslie Vaughan. Many of us have much to thank them for.

It was about fifteen years ago that a small body of men came to discuss the development of a forum where those with an interest in the animal nervous system could meet to exchange ideas, learn and inspire. The European Society for Veterinary Neurology thus came about and was one of the first specialty groups in Europe. It has largely metamorphosed into the European College of Veterinary Neurology, which is a highly successful organisation providing a training framework for the neurologist of the future, and which has close associations with its elder sister organization in the United States, the ACVIM (Neurology) College.

Today, veterinary neurology is a flourishing specialization in Europe, the United States and worldwide. Many pet owners now expect to be offered expert care for their animals, and neurologists practice in many teaching hospitals and referral clinics. It is perhaps with prescience that the veterinary intellectuals of the recent past led to the development of organisations that are now satisfying the needs of our customers – the general practicing veterinarian, clients and their pets.

This third edition of *Manual of Canine and Feline Neurology* sees many changes from the first two editions, which I was privileged to edit. Many contributions are made by a new guard of veterinary neurologists, who doubtless have the time, drive and desire to review and précis literature, take up new ideas and try them out in the clinic. In time they will doubtless go on to train the clinicians of the future. It is worth remembering that many ideas that today are promoted as being *de rigueur* have their basis in research and experience long published and long forgotten.

Enjoy this book and gain experience wherever it is available.

Simon J Wheeler BVSc PhD DipECVN DipIMgmt FRCVS
Editor of the BSAVA Manual of Small Animal Neurology, 1st and 2nd editions

## **Preface**

The third edition of the BSAVA Manual of Canine and Feline Neurology has been completely rewritten and restyled since the last edition was published in 1995. The changes reflect the rapid and extensive additions to this field of veterinary medicine that have taken place over the last 10 years. In addition to documenting the advances of knowledge in neurology, this manual has expanded the problem-oriented approach taken in the first two editions.

The advent of more routine access to advanced imaging modalities, such as magnetic resonance imaging (MRI), has greatly expanded neurological knowledge and enabled a more definitive work-up of the neurological case to be performed. However, such advancements have complicated the decision-making processes that we undertake on a daily basis for neurology cases, as it has become imperative to understand which diagnostic modality is indicated for each case. The improved sensitivity of MRI increases the need to perform a thorough and accurate clinical evaluation of the patient in order to avoid misinterpretation of clinically insignificant lesions visible on MR images. In developing a new version of the Neurology Manual we were very aware that such decision-making processes need to be clear and logical. Despite the recent advances in knowledge and diagnostic techniques, it remains essential to approach the neurological patient in a consistent manner; performing the neurological examination, localizing the lesion, and developing a list of differential diagnoses; from this point, a diagnostic, treatment and prognostic plan can be formulated.

The new edition of the Manual retains the basic layout of the old editions; as before, the first section refers to the essentials of neurological diagnosis and is followed by a section on neurological presentations. The third section is a new section entitled Therapeutics. The first section contains the information necessary for working-up the neurological patient and includes neurological examination, lesion localization, clinical pathology, electrophysiology and neuroradiology chapters. The neuroradiology chapter retains thorough descriptions of radiographic techniques that can be performed in a typical small animal practice in addition to providing a concise and beautifully illustrated update on the most advanced imaging techniques available. A new chapter in this section addresses the topic of biopsy of the CNS and neuromuscular systems, covering the indications for such procedures in addition to the utility of these procedures.

The second section of the manual has been expanded with the addition of several new chapters on different presenting problems. This has been necessary due to the overwhelming increase in information now available on both new and previously described diseases. The aim of this approach is to assist the busy practitioner in identifying the area of the nervous system responsible for their patient's signs, for example, head tilt or tremors. The reader is then guided through an appropriate diagnostic approach and the different diseases to be considered. Each chapter in this section presents the diseases in a similar fashion, detailing the clinical presentation, pathogenesis, diagnosis, treatment and prognosis of each disease.

The third section of the manual contains completely new chapters devoted to the special treatment considerations necessary for the neurological patient. The chapters include emergency neurology presentations, (detailing spinal trauma, head injury and status epilepticus), neuroanaesthesia, clinical pharmacology, radiotherapy, neurosurgery (indications and complications), and rehabilitation of the neurological patient.

As neurology is such a visual subject to teach and learn, we have endeavoured to illustrate the manual carefully to make it both visually pleasing and to explain clearly the key areas of neuroanatomy and disease pathogenesis. It goes without saying that these illustrations and photographs accompany some very high quality text written by neurology specialists from around the globe.

Understanding of veterinary neurology continues to grow and the practice of clinical neurology to evolve. We have endeavoured to put together a valuable 'stepping-stone' toward furthering understanding of this difficult subject at this present time. It would, though, have never been possible without significant and inspiring work done in the past, with particular reference to the previous editions of this manual by Dr Simon Wheeler. Our thanks extend to him, as well as the contributing authors for their time and expertise, to the illustrator Allison Wright for her beautiful images and to the BSAVA team, especially Nicola Lloyd and Marion Jowett, for their patience with us.

We hope you enjoy it.

Simon Platt Natasha Olby

July 2004

## The neurological examination

## **Laurent Garosi**

## Aims of the neurological examination

The aims of the neurological evaluation of a patient are to answer the following questions:

- 1. Do the clinical signs observed refer to a nervous system lesion?
- 2. What is the location of this lesion within the nervous system?
- 3. What are the main types of disease process that can explain the clinical signs?
- 4. How severe is the disease?

The first two questions are answered by the neurological examination and aim to determine the anatomical diagnosis (location and distribution of the lesion within the nervous system). The third question is answered by compiling the information on the patient's signalment and history of the problem with the anatomical diagnosis, to determine the differential diagnosis. Disease severity can help the clinician to determine the eventual prognosis of the conditions considered in the differential diagnosis. Diagnostic tests are then carried out. The choice and interpretation of these tests must rely on a clear knowledge of the lesion localization within the nervous system and the expected disease processes.

## History

Taking an accurate and complete history is the first step in the neurological evaluation (Figure 1.1). A detailed neurological examination form is presented in Figure 1.2.

### Signalment

The signalment includes species, age, breed, sex and coat colour. Many neurological disorders have an age and breed predilection that should be considered when forming a differential diagnosis for a particular problem (see Appendix 1). Similarly, genetic neurological disorders can be related to coat colour.

## Chief complaint

The chief complaint is the reason the owners sought medical assistance. The owners must be encouraged to give a clear and concise description of their concern.

### **General information**

Confirmed age of patient

Sibling numbers and health

How long the owner has cared for the pet

Vaccination status (type of disease vaccinated for and time since last vaccination)

Travel history

Travernistory

Parasite treatments (including fleas and worms)

Access to toxins

History of trauma

Environment

Health of other animals in the same household

Diet, including supplementary therapies

Current or recent medication

Medical or surgical history

Drug allergies

## Specific complaint

Detailed description of the chief complaint:

When did it start?

How did it start?

How has it altered since onset?

Is pain a feature?

Has medication been associated with a change in the condition?

### Systemic health

Appetite and thirst

Vomiting/regurgitation/diarrhoea/coughing/sneezing

Urinary and faecal continence

Bodyweight change

Exercise tolerance

Assessment of vision

Important information to obtain from the owner of a neurological patient.

The precise meaning of the words used to refer to the chief complaint must be clarified to prevent any ambiguity and, ultimately, misdiagnosis. This is particularly important when the chief complaint is a paroxysmal event such as an epileptic seizure, loss of balance, or collapse. In the absence of clinical findings, the owners' description of the event might be the sole basis for establishing an anatomical and differential diagnosis. Video footage of such an event could offer valuable information and clarify many ambiguities. The onset, evolution and course of the illness are of paramount importance and may provide insight into specific differentials (see Chapter 2).

Chief complaint	
Historical background  Onset Duration Evolution Static/Progressive/Regressive Wax and wane/Episodic Lateralization of signs  Animal background Previous medical problems Previous surgical problems Previous travel Vaccination status Diet Family history	Neurological findings  Neurological exam? Normal/Abnormal  Abnormalities Neurolocalization  Is the lesion?:  Focal Multifocal Diffuse  Symmetrical Asymmetrical
Treatment	
Anatomical diagnosis Focal M	lultifocal Diffuse
☐ Forebrain ☐ Brainstem ☐ Cerebellar ☐ Vestibular: peripheral/central ☐ C1-C5 ☐ C6-T2 ☐ T3-L3	☐ L4-L6 ☐ L6-S3 ☐ Neuromuscular ☐ Mononeuropathy ☐ Polyneuropathy ☐ Junctionopathy ☐ Myopathy
Suspected aetiological diagnosis	
<ul> <li>□ Degenerative</li> <li>□ Anomalous</li> <li>□ Metabolic</li> <li>□ Neoplastic</li> <li>□ Nutritional</li> </ul>	<ul> <li>□ Inflammatory/infectious</li> <li>□ Idiopathic</li> <li>□ Trauma</li> <li>□ Toxic</li> <li>□ Vascular</li> </ul>
Recommended diagnostic tests	

## Observation

Mental status Normal/Abnormal Confusion/Depressed/Stuporous/Comatose

Behaviour

Normal/Abnormal

Body posture

Normal/Abnormal

Head tilt/Head turn/Spinal curvature/ Wide-based stance/Decerebrate/ Decerebellate/Schiff-Sherrington

Gait

Normal/Abnormal

Ataxia

Symmetrical/Asymmetrical

Thoracic/Pelvic limbs

Paresis/plegia

Tetra/Para/Mono/Hemi

Circling Lameness Left/Right

Involuntary movement

## **Cranial nerves**

Left

Right

Facial symmetry

Palpebral (V + VII)

Corneal

(V + VI, VII)

Oculovestibular

(VIII + III, IV, VI)

Jaw tone

(V)

Gag reflex

(IX, X)

Tongue

(XII)

Menace

(Retina, II, forebrain + cerebellum, VII)

Nasal stimulation

(V, forebrain)

Pupil size

(Retina, II + III)

S M L In light

ML In dark

(Sympathetic)

Pupillary light reflex

(Retina, II + III)

Left eye

Right eye

Nystagmus Spontaneous

R (VIII)

R

SML

SML

V R

Positional

Strabismus

Permanent

(III or IV or VI)

Positional

(VIII)

## Postural reactions

Left

Right

Proprioceptive positioning

Thoracic

Pelvic

Hopping

Thoracic

Pelvic

Wheelbarowing

Extensor postural thrust

Visual placing

Tactile placing

## Spinal reflexes

Left

Right

Withdrawal thoracic

(C6-T2)

Extensor carpi radialis

(C7-T2)

Withdrawal pelvic

(L6-S2)

Patellar

(L4-L6)

Gastrocnemius

(L6-S1)

Perineal

(S1-S3)Tail movement?

Y/N

## **Urinary function**

Evidence of voluntary urination?

Y/N

Bladder distended? Easy bladder expression? Y/N Y/N

## Sensory evaluation

Left

Deep pain perception

Right

**Thoracic** 

Pelvic

Perianal

Panniculus Cutaneous sensation

**Thoracic** 

Pelvic

Specific nerve affected?

## Palpation/manipulation

Spinal pain?

Cerv/Thor/Lumb/Sacral

Joint pain?

Y/N

Muscle pain?

Y/N

Neck movement

Normal/Abnormal

(continued) An example of a comprehensive neurological examination form. H = horizontal; L = large;M = mid-range; R = rotatory; S = small; V = vertical.

Through careful questioning, the onset should be defined as:

- Acute (onset over minutes to hours)
- Subacute (onset over days)
- Chronic (onset over several days, weeks or months)
- Episodic (animal returns to normal between episodes).

The evolution of the condition should be recognized as progressive, static, improving, or waxing and waning. It is also important to identify factors that trigger or improve the signs, and previous therapy and its effect on disease course.

## Animal's background

After determining the chief complaint, collecting the history should end with general information regarding any previous medical or surgical conditions, family history, vaccination status, diet, previous travel history, concurrent drug use and drug reactions, and the animal's environment (i.e. access to toxins).

## **General physical examination**

In all patients, the neurological examination should be preceded by a thorough general physical examination of all other body systems. This is essential in detecting an abnormality in other body systems: that might also affect the nervous system (e.g. animals with liver disease presented for epileptic seizures and abnormal mentation); that mimic a primary neurological disorder (e.g. bilateral cranial cruciate ligament rupture in an animal presented for a pelvic limb gait abnormality); or that could influence the prognosis (e.g. bladder rupture in an animal with a traumatic spinal fracture). A thorough orthopaedic examination is particularly important in animals with gait disturbances.

## **Neurological examination**

A general overview of the neurological examination ispresented in Figure 1.3 (see Figure 1.2 for a comprehensive examination form). Sedation, analgesia or neurological conditions such as epileptic seizures can transiently influence the results of this neurological evaluation.

## Part I: Observation

Mental status and behaviour Posture and body position at rest Evaluation of gait Identification of abnormal involuntary movements

## Part II: Hands-on examination

Cranial nerve assessment
Postural reaction testing
Spinal reflexes; muscle tone and size
Sensory evaluation

1.3

Overview of the neurological examination.

## **Part I: Observation**

## Mental status and behaviour

Anatomy and function: Two anatomical structures are involved in maintaining wakefulness (a state in which the individual is fully aware of its environment). These are the ascending reticular activating system (ARAS) within the brainstem, and the cerebral cortex. The ARAS receives sensory information from the spinal cord and the cranial nerves. It then projects stimulatory input diffusely to the cerebral cortex to maintain a state of consciousness. The portion of the forebrain commonly associated with behaviour is the limbic system, consisting of portions of the cerebrum and diencephalon (see Chapter 8).

Clinical signs: Mentation can be observed initially while taking the history. Abnormal mental status can be classified as depressed, stuporous, comatose or delirious (also known as encephalopathic or inappropriate) (Figure 1.4). Altered states of consciousness are usually related to abnormal brain function (forebrain or ARAS) but animals that have severe systemic illness can appear depressed and it is important to establish the usual behaviour of each individual animal from the owner. Coma usually results from interruption of the ARAS in the brainstem.

Status	Clinical signs	
Confused and disorientated (delirious)	Responding to environmental stimuli in an inappropriate manner	
Normal	Alert, with a normal response to environmental stimuli	
Depressed	Drowsiness, inattention and less responsive to environmental stimuli	
Stuporous	State of unconsciousness with reduced responses to external stimuli but can be roused by a painful stimulus	
Comatose State of unconsciousness with absence response to any environmental stimuli, including pain		

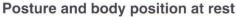
1.4

Classification of level of consciousness.

Common changes in behaviour include aggression, compulsive walking, loss of learned behaviour (e.g. loss of toilet training), vocalizing or head pressing (Figure 1.5). Hemi-neglect syndrome, also known as hemi-inattention syndrome, refers to an abnormal behaviour in which animals with structural forebrain disease ignore sensory input from one half of their environment (e.g. eating from one half of the bowl, turning in the wrong direction in response to sound). This syndrome indicates a forebrain lesion on the side contralateral to the side apparently 'ignored' by the animal.



Head pressing in a 9-year-old neutered female Staffordshire Bull Terrier with a thalamic brain tumour.



The posture and body position at rest should be evaluated and determined as being normal or abnormal. Common abnormalities encountered are as follows.

### Head tilt

This abnormal head posture is characterized by a rotation of the median plane of the head (one ear is held lower than the other) (Figure 1.6). A head tilt often indicates a vestibular disorder (peripheral or central). The head is usually tilted toward the same side as the lesion. Lesions affecting the cerebellar portion of the vestibular apparatus (cerebellar peduncle or flocculo-nodular lobe) can cause a central vestibular syndrome with a paradoxical head tilt (i.e. head tilted to the contralateral side of the lesion).



1.6 Severe head tilt in a 3-year-old neutered female Japanese Chin with a vestibular syndrome caused by granulomatous meningoencephalitis.

## Head turn

In contrast to a head tilt, the median plane of the head remains perpendicular to the ground but the nose is turned to one side. A head turn is often associated with body turn (pleurothotonus) (Figure 1.7) and circling. These signs (called aversion syndrome) are usually toward the side of a forebrain lesion.



Right-sided head and body turn (pleurothotonus) in a 10-year-old male Staffordshire Bull Terrier with a right-sided forebrain tumour.

### Spinal curvature

This can be congenital or acquired, and permanent or intermittent. The aetiology is not always discernible. Common lesions include:

- Malformed vertebrae (e.g. hemivertebrae)
- Intraparenchymal spinal cord disease (e.g. syringohydromyelia) causing denervation of the associated paraspinal musculature, producing asymmetrical muscle tension and subsequent vertebral deviation
- Spinal pain (e.g. disc herniation) (Figure 1.8).



Low head carriage and severe neck pain caused by cervical intervertebral disc herniation in a 6-year-old neutered female mixed-breed dog.

Spinal curvatures are commonly classified as:

- Scoliosis (lateral deviation of the spine)
- Lordosis (ventral curvature of the spine)
- Kyphosis (dorsal curvature of the spine)
- Torticollis (twisting of the neck).

These are not specific for disease aetiology.

## Decerebrate rigidity

This posture is observed as a result of a rostral brainstem lesion (between the colliculi of the midbrain). It is characterized by extension of all limbs and opisthotonus (extension of the head and neck) associated with a stuporous or comatose mental status (Figure 1.9).



Decerebrate rigidity in a 4-year-old male French Bulldog with caudal subtentorial brain herniation associated with a large frontal lobe brain tumour.



The rostral part of the cerebellum inhibits the stretch reflex mechanism of antigravity muscles (extensor muscle tone). Lesions at this level can result in opisthotonus with the thoracic limbs extended (decerebellate posture). Compared with decerebrate posture, the hips may be flexed by the increased tone in the iliopsoas muscles, and the mentation remains normal. This posture is often caused by an acute cerebellar lesion (Figure 1.10) and can sometimes be episodic.



1.10 Decerebellate rigidity in an adult crossbreed with a cerebellar infarct.

## Schiff-Sherrington posture

This posture is observed with an acute severe thoracic or cranial lumbar spinal cord lesion in dogs. Such a lesion may interfere with inhibitory ascending neurons (also known as border cells) that project cranially from the lateral grey matter of the cranial lumbar spinal cord segments to inhibit the thoracic limb extensor motor neurons. This posture consists of an extensor hypertonia of the thoracic limbs, with retention of voluntary movements and normal conscious proprioception in these limbs, in addition to paralysis of the pelvic limbs (Figure 1.11). Classically, pelvic limb paralysis is hypotonic, despite the fact that the paralysis is caused by direct interference with the upper motor neuron (UMN); however, the reflexes are intact in these limbs. In practice, this decrease in tone is transient and by the time the animal is pre-



Schiff–Sherrington posture in a Labrador with a thoracolumbar spinal fracture/luxation.

sented to the veterinary surgeon, pelvic limb tone has returned. This sign is present only in acute lesions but does not have prognostic significance.

## Wide-based stance

This posture is characteristic of a balance disorder with diseases particularly affecting the cerebellum.

## **Evaluation of gait**

Gait disturbances are one of the most common neurological presentations. One of the first stages of the neurological examination involves assessing the animal's ability to make coordinated movements. Examination of the gait should be done in a place where the patient can be allowed to move freely. This is best accomplished by having the owner walk the animal over a non-slip surface. If the animal is not making any attempt to walk, body support (such as a sling or harness) should be provided, as necessary, so that any subtle voluntary movement can be detected. A normal gait requires intact function of the brainstem, cerebellum, spinal cord and sensory and motor peripheral nerves, neuromuscular junctions and muscles. The cerebrum's contribution to the gait is less important in dogs and cats than in primates. An abnormal gait may be due to an abnormality of: coordination (ataxia); the strength of the voluntary movement (paresis); or (more often) a combination of the two.

### **Ataxia**

Ataxia is defined as an uncoordinated gait. This deficit can arise from:

- An afferent kinaesthetic deficit in the peripheral nerve or spinal cord (proprioceptive or sensory ataxia)
- A vestibular disorder (vestibular ataxia)
- A cerebellar disorder (cerebellar ataxia) (Figure 1.12).

Ataxia can be further divided into:

- Hypometria (shorter protraction phase of gait)
- · Hypermetria (longer protraction phase of gait)
- Dysmetria (ability to control the distance, power and speed of an action is impaired. When applied to limb movements, it may describe a combination of both hypo- and hypermetria).

Type of ataxia	Neurolocalization	Clinical signs	
Proprioceptive	General proprioceptive pathways: Peripheral nerve Dorsal root Spinal cord Brainstem Cerebral cortex	Abnormal postural reactions with limb paresis	
Vestibular	Vestibular apparatus: Vestibular nuclei (central) Vestibular portion of CN VIII or vestibular receptors (peripheral)	Head tilt, leaning, falling or rolling to one side, abnormal nystagmus, strabismus, normal (peripheral) or abnormal (central) postural reactions  Crouched posture, reluctance to move and wide head excursion in case of bilateral dysfunction	
Cerebellar	Cerebellum	Wide-based stance, intention tremors of the head, loss of balance and truncal sway, dysmetric gait, pendular nystagmus, delayed ons and dysmetric hopping reactions, ipsilateral menace deficit with normal vision, absence of limb paresis and conscious proprioceptio deficits, and normal mentation (pure cerebellar disease)	

1.12

Classification and criteria for differentiation of ataxia.

### **Paresis**

Paresis is defined as a weakness or inability to generate movement voluntarily. The term paresis implies that some voluntary movement is still present; paralysis (-plegia) refers to a more severe paresis with complete loss of voluntary movement. Depending on which limbs are affected, the terms can be further defined:

- Tetraparesis/tetraplegia: paresis/paralysis of all four limbs resulting from a lesion located cranial to the T3 spinal cord segment or from a generalized lower motor neuron (LMN) disorder
- Paraparesis/paraplegia: paresis/paralysis of the pelvic limbs caused by a lesion caudal to T2
- Monoparesis/monoplegia: paresis/paralysis of one limb, usually caused by a lesion of the LMN innervating the affected limb; very lateralized lesions caudal to T2 can also result in monoparesis
- Hemiparesis/hemiplegia: paresis/paralysis of the limbs on one side due to a lesion located cranial to T2. This hemiparesis/plegia is ipsilateral to a lesion located between T2 and the caudal midbrain, and contralateral to a lesion located in the rostral midbrain or cerebrum.

There are two types of paresis: UMN and LMN, causing a spastic or flaccid paresis, respectively (see Spinal reflexes). The severity of the gait impairment increases as the lesion occurs more caudally in the central nervous system (CNS). Brainstem or spinal cord lesions result in an obvious gait abnormality, while forebrain lesions usually cause only subtle gait abnormalities.

## Circling

Circling can be caused by lesions in the vestibular system or by an asymmetrical or focal lesion in the forebrain. Tight circles are usually but not exclusively associated with a vestibular disorder, while wide circles are often associated with a forebrain lesion. With vestibular disease, circling is associated with other signs of vestibular involvement (head tilt, nystagmus, strabismus or falling) and is usually ipsilateral to the lesion (except with lesions affecting the caudal cerebellar peduncle, fastigial nucleus and flocculonodular lobes of the cerebellum). Circling is usually toward the side of a focal or asymmetrical forebrain lesion.

### Lameness

Lameness usually presents with a short stride on the affected limb and long stride on the contralateral limb, and is usually associated with pain from orthopaedic disease. Additionally, it can be associated with nervous system dysfunction referred to as 'nerve root signature' (referred pain down a limb, causing lameness or elevation of the limb, resulting from entrapment of the spinal nerve, usually by a lateralized disc extrusion or nerve root tumour).

## Identification of abnormal involuntary movements

## **Tremors**

Tremors (see Chapter 12) are defined as a synchronous involuntary oscillating contraction of antagonistic muscle groups. They can affect all or part of the body and can be classified as resting tremors, intention tremors (occur as the animal intends to move) or action tremors (occur as parts of the body are maintained in certain positions). Generalized tremors are more commonly encountered. Intention tremors are exaggerated by goal-oriented movements, such as eating, and most often constitute a dysmetria of the head movement associated with cerebellar disease.

## **Epileptic seizure**

An epileptic seizure (see Chapter 7) is the clinical manifestation of excessive or hypersynchronous electrical activity in the cerebral cortex. It can be focal or generalized. An epileptic seizure implies a forebrain disorder. Its cause may originate from outside or inside the brain.

## Myoclonus

Myoclonus (see Chapters 8 and 17) is a repetitive rhythmic contraction of a group of skeletal muscles, producing a quick jerking movement of a body part. Myoclonus can be the result of encephalitis or myelitis caused by distemper virus in dogs but is not a pathognomonic sign.

## Myotonia

Myotonia (see Chapter 17) is a sustained irregular contraction with delayed relaxation of a muscle or group of muscles following voluntary contraction. It occurs in certain congenital and acquired muscle disorders and is often asynchronous and asymmetrical.

## Cataplexy

Cataplexy (see Chapter 17) is a paroxysmal onset of flaccid paralysis (muscle atonia) with preservation of consciousness, lasting for a few seconds to a few minutes. The attacks are frequently induced by excitement (such as eating, playing or the presence of the owner or another dog) and can be reversed by an external stimulus. Cataplexy can be accompanied by narcolepsy.

## Head 'bobbing'

Intermittent head bobbing is a common complaint often seen in particular breeds such as the Bulldog and Dobermann Pinscher. It can occur as an idiopathic disorder or as a consequence of structural brain disease (especially with pathology affecting the thalamus).

## **Part II: Hands-on examination**

## Cranial nerve assessment

Tests of cranial nerve (CN) function are summarized in Figure 1.13. The following is an overview of each

cranial nerve's function, clinical evaluation and signs of dysfunction. Testing of these nerves should be done in conjunction with the assessment of conscious proprioception and mentation to determine whether there is brainstem disease or peripheral nerve disease.

## Olfactory nerve - CN I

Anatomy and function: CN I is involved in the conscious perception of smell. It is a unique sensory cranial nerve, in that its cell bodies lie in the olfactory epithelium on the ethmoturbinate bones rather than in a ganglion. Its axons pass through the cribriform plate to synapse with secondary neurons in the olfactory bulb. These secondary neurons pass successively into the olfactory peduncle and olfactory tracts before they synapse with third order neurons in the olfactory tubercle. This final neuron projects to the piriform lobe in the olfactory region of the brain.

Clinical evaluation: Evaluation of smell is difficult in animals and remains a subjective assessment. This sensory function can be assessed by testing the animal's response (sniffing or licking of the nose, aversion of the head) to aromatic substances whilst blindfolded. Care should be taken not to use irritating substances that could stimulate the trigeminal nerve and cause similar responses.

Clinical signs of dysfunction: Decreased or absent sense of smell is defined as hyposmia or anosmia, respectively. Detecting deficits in smell is difficult and often based on historical findings (e.g. decreased appetite). Non-neurological causes (such as rhinitis and other nasal disease) are more common causes than CNS disease.

Cranial nerve test	Afferent cranial nerve	Intermediate brain region	Efferent cranial nerve	Principal effect noted
Palpebral reflex	CN V – Trigeminal (ophthalmic or maxillary)	Brainstem	CN VII - Facial	Blink elicited by touching of the medial or lateral canthus of the eye
Corneal sensation	CN V – Trigeminal (ophthalmic)	Brainstem	CN VII - Facial CN VI - Abducent	Blink and globe retraction elicited by touching the cornea
Vestibulo-ocular reflex	CN VIII – Vestibulocochlear	Brainstem	CN III - Oculomotor CN IV - Trochlear CN VI - Abducent	Nystagmus induced by moving the head
Menace response	CN II – Optic	Forebrain Cerebellum Brainstem	CN VII - Facial	Blink elicited by a menacing gesture
Response to stimulation of nasal mucosa	CN V – Trigeminal (ophthalmic)	Forebrain Brainstem	None	Withdrawal of the head elicited by touching the nasal mucosa
Pupillary light reflex	CN II – Optic	Brainstem	CN III – Oculomotor	Pupillary constriction elicited by shining a light in the eye
Gag reflex	CN IX – Glossopharyngeal CN X – Vagus	Brainstem	CN IX – Glossopharyngeal CN X – Vagus	Contraction of the pharynx elicited by its palpation

.13 Important cranial nerve tests.

## Optic nerve - CN II

**Anatomy and function:** The optic nerve is not a 'true' nerve but an extension of the brain. It is part of the central visual pathway (involved in sensory visual perception) and the afferent component of the menace response and pupillary light reflex (PLR).

The visual pathway (see Chapter 9) involves three consecutive neurons.

- The first neuron represents the bipolar cells of the retina and receives visual information from the neuroepithelial cells of the retina (e.g. rods and cones).
- The second neuron corresponds to the ganglion cell of the retina. Its axon lies in the optic nerve and continues through the optic chiasm and proximal part of the optic tract of the opposite side (55% decussation in humans, 66% in cats, 75% in dogs).
- The third neuron has its cell body in the lateral geniculate nucleus in the diencephalon. Its axon projects to the visual cortex (mostly contralateral occipital cortex) in a band of fibres called the optic radiation.

The menace response (Figure 1.14) is a cortically mediated blink produced by a threatening or unexpected image suddenly appearing in the near visual field. It is present from about 10–12 weeks of age in dogs and cats. The afferent part of this response involves the same structures as the visual pathways. The efferent part of the response is not well understood. The information generated in the visual cortex is forwarded to the



The menace response is elicited by making a threatening gesture at the eye. The afferent pathway is in the retina, optic nerve, contralateral optic tract and visual cortex. The efferent pathway involves the contralateral motor cortex, the ipsilateral cerebellar cortex and facial nerve (CN VII). The expected response is a closure of the eyelid. The contralateral eye must be blindfolded with the other hand to assess each eye separately. Care must be taken not to touch the eyelashes or to create air currents that might stimulate sensation of the face (CN V, trigeminal nerve) and elicit a palpebral or corneal reflex.

motor cortex to initiate a motor response. The corticobulbar pathways to the facial nerve nucleus (CN VII) then transmit the motor information. This response requires intact facial nerve function as well as an intact cerebellum (ipsilateral function). The neuronal pathways through the cerebellum are not known.

The afferent part of the PLR shares some common pathways (up to the level of the optic tract) with the visual pathways. While axons involved in vision reach the conscious level after synapse with the lateral geniculate nucleus, the axons involved in the PLR synapse with a third neuron in the pretectal nucleus. Most of the axons arising from this nucleus decussate again and synapse in the parasympathetic component of the oculomotor nucleus (ipsilateral to the stimulated eye) in the mesencephalon. There are also neurons that do not decussate and which project to the oculomotor nucleus on the contralateral side to the stimulated eye. The majority of axons decussate and this explains why the direct response (constriction in the eye receiving the light stimulus) is greater than the consensual response (constriction in the eye not receiving the light stimulus). The efferent arm of the PLR involves parasympathetic axons in CN III (oculomotor), causing constriction of the pupil.

Clinical evaluation: The optic nerve is the common component of the afferent pathways involved in vision. menace response, visual placing and the PLR. These tests use different integration centres within the brain and different efferent pathways. The integrity of the optic nerve can be determined by combining the results of these tests. Vision in animals is evaluated by observation of the animal navigating an obstacle course (animal walking into or avoiding obstacles) and by testing the menace response. If unilateral visual loss is suspected, each eye can be blindfolded in turn prior to completion of the obstacle course. The PLR tests the integrity of the optic nerve to the level of the lateral geniculate nucleus but does not test the animal's vision. The PLR should therefore be performed in all blind animals to determine the location of the lesion. Fundic examination and evaluation of the appearance of the optic disc are also important parts of the evaluation of the optic nerve (see BSAVA Manual of Canine and Feline Ophthalmology).

**Clinical signs of dysfunction:** Lesions of the optic nerve can be manifest as partial or complete loss of vision and/or dilated and unresponsive pupils (see Chapter 9).

## Oculomotor nerve - CN III

Anatomy and function: CN III innervates the ipsilateral dorsal, ventral and medial recti extraocular muscles as well as the ventral oblique muscle. The oculomotor nerve also plays an important role in the efferent arm of the PLR and eyelid movement. It is involved in the elevation of the upper eyelid (levator palpebrae superioris) and controls pupillary constriction via its parasympathetic component. The oculomotor nuclei are located in the rostral mesencephalon. Their axons exit the brainstem and traverse the cavernous sinus lateral to the hypophysis before they exit the skull through the orbital fissure.

Clinical evaluation: CN III function can be assessed by observing the eye position and movements at rest and by testing for normal physiological nystagmus (vestibulo-ocular reflex) by moving the head from side to side as well as up and down (see Vestibulocochlear nerve – CN VIII). The parasympathetic function of CN III can be assessed by observation of the pupil size (Figure 1.15) and evaluation of the PLR.



Pupil symmetry can be assessed using the indirect ophthalmoscope. The animal should be examined in room light as well as in darkness to evaluate the ability of the pupils to constrict (parasympathetic function) and to dilate (sympathetic function), respectively.

Clinical signs of dysfunction: Lesions of the oculomotor nerve produce a ventrolateral strabismus and an inability to rotate the eye dorsally, ventrally or medially during oculovestibular testing (external ophthalmoplegia) (Figure 1.16). This strabismus must be differentiated from a vestibular strabismus that only occurs in certain head positions and is termed positional strabismus. The above signs can also be associated with a dilated unresponsive pupil (referred to as internal ophthalmoplegia) and/or narrowing of the palpebral fissure (ptosis of the upper eyelid).



Lateral strabismus in an 8-year-old female neutered Rottweiler with a cavernous sinus meningioma. The compression of the oculomotor nerve (CN III) by this tumour is causing paralysis of the medial, dorsal and ventral recti and ventral oblique muscles. The net result is a lateral deviation of the eyeball. The eyeball failed to adduct when testing the normal physiological nystagmus. Compared with a vestibular strabismus (which depends on the head position), this type of strabismus is visible whatever the position of the head.

### Trochlear nerve - CN IV

Anatomy and function: CN IV innervates the contralateral dorsal oblique muscle. This muscle is responsible for inward rotation of the eyeball. The trochlear nucleus is located in the caudal mesencephalon. After leaving the brainstem, its axons decussate on the dorsal surface of the brainstem and course rostrally through the cavernous sinus before they exit the skull via the orbital fissure.

*Clinical evaluation:* As for CN III, CN IV can be assessed by observation of the eye position at rest and by testing for normal physiological nystagmus.

Clinical signs of dysfunction: Lesions of the trochlear nerve produce a dorsolateral strabismus (extorsion) of the contralateral eye. In dogs this is best evaluated by fundoscopic examination, observing temporal deviation of the dorsal retinal vessels. In cats, it can be seen by alteration of pupil orientation. This is a very rare isolated finding: lesions of this nerve usually occur in combination with lesions of CN III and CN VI, producing complete ophthalmoplegia.

## Trigeminal nerve - CN V

Anatomy and function: CN V provides sensory innervation of the face (cutaneous elements of the face as well as the cornea, mucosa of the nasal septum and mucosa of the oral cavity) and motor innervation of the masticatory muscles (temporalis, masseter, medial and lateral pterygoid and rostral part of the digastric muscles). The cell body of the sensory part of CN V lies in the trigeminal ganglion. Its sensory nuclei form a large separate continuous and elongated nuclear column extending along the brainstem. Its motor nuclei are located in the pons. CN V consists of three branches: ophthalmic, maxillary and mandibular. Each branch provides sensation to specific areas of the face:

- Ophthalmic (cornea, medial canthus of the eye, nasal septal mucosa and skin on the dorsum of the nose)
- Maxillary (lateral canthus of the eye, skin of the cheek, side of the nose, muzzle, palates, mucous membrane of the nasopharynx, teeth and gingiva of the upper jaw)
- Mandibular (mandibular portion of the face and oral cavity).

The ophthalmic and maxillary branches are in close proximity to the cavernous sinus before they exit the skull through the orbital fissure and round foramen, respectively. These two branches have only sensory function. The mandibular branch exits the skull through the oval foramen and serves both a motor and sensory function.

*Clinical evaluation:* The motor function of CN V is assessed by evaluating the size and symmetry of the masticatory muscles and testing the resistance of the jaw to opening the mouth (Figure 1.17). The sensory function (sensation of the face) can be individually tested by:

- The corneal reflex (ophthalmic branch)
- The palpebral reflex (ophthalmic or maxillary branch when touching the medial or lateral canthus of the eye, respectively) (Figure 1.18)
- The response to stimulation of the nasal mucosa (ophthalmic branch) (Figure 1.19)
- Pinching the skin of the face with haemostat forceps and observing an ipsilateral blink or facial twitch (Figure 1.20).

A reflex response is best distinguished from a conscious response by stimulating the nasal mucosa: the normal animal will pull its head away, while the animal with forebrain disease may blink or show a facial twitch, but not show a conscious reaction.



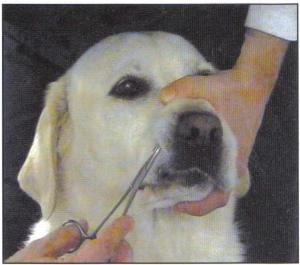
1.17 Assessing the resistance of the jaw on opening of the mouth (jaw tone) tests the motor function of the trigeminal nerve (CN V).



Touching the medial or lateral canthus of the eye and observing for a blink test (the palpebral reflex). The afferent arm of this reflex is mediated by the trigeminal nerve (CN V) (facial sensation) while the efferent arm is mediated by the facial nerve (CN VII) (closure of the eyelid).



The response to stimulation of the nasal mucosa is a cortically mediated withdrawal of the head. The afferent arm is mediated by the trigeminal nerve (CN V). The integration of this response occurs in the contralateral forebrain. Both sides should be carefully assessed to evaluate possible asymmetry.



Observing a curl of the lip as it is pinched indicates that the afferent arm (CN V – trigeminal nerve) and efferent arm (CN VII – facial nerve) of this reflex are intact. Depending on the intensity of the stimulation, a behavioural response (vocalization, turning of the head) may also be observed (cortically mediated response). Both sides must be assessed to evaluate possible asymmetry. Occasionally, decreased perception of facial sensation (hypoalgesia) can be observed in animals with contralateral forebrain disease. In such cases, the animal curls its lip (normal reflex arc) but fails to show a behavioural response after stimulation of the lip contralateral to the lesion (abnormal response).

Clinical signs of dysfunction: Unilateral involvement of the motor part of CN V causes ipsilateral masticatory muscle atrophy (Figure 1.21) and decreased jaw tone. Enophthalmia and protrusion of the third eyelid can be observed in the ipsilateral eye (passive retraction of the eyeball due to the loss of the temporalis muscle mass). Bilateral involvement of the motor branches produces a dropped jaw with inability to close the mouth voluntarily (Figure 1.22), associated with various degrees of



Unilateral temporalis and masseter muscle atrophy in a 9-year-old male Labrador with a trigeminal nerve sheath tumour. The ipsilateral enophthalmia is caused by the loss of the temporalis muscle bulk and therefore passive retraction of the eyeball.



Dropped jaw and inability to close the mouth in a 5-year-old neutered female Cocker Spaniel with idiopathic trigeminal neuritis.

masticatory muscle atrophy depending on the duration of signs. Decreased or complete loss of facial sensation is defined as facial hypoaesthesia or anaesthesia. Involvement of the ophthalmic branch of CN V can also produce decreased tear secretion and neurotropic keratitis secondary to the loss of afferent stimulation to the lacrimal reflex (see Chapter 9).

## Abducent nerve - CN VI

**Anatomy and function:** CN VI innervates the ipsilateral lateral rectus and retractor bulbi muscles. The CN VI nucleus is located in the rostral medulla oblongata. Its axons follow the same pathway as the axons of CN III and CN IV. The abducent nerve leaves the cranial cavity through the orbital fissure.

Clinical evaluation: CN VI function can be assessed: by observation of the eye position and movement at rest; by testing for normal physiological nystagmus; and by testing for normal eyeball retraction during the corneal reflex.

Clinical signs of dysfunction: Lesions of the abducent nerve result in: an ipsilateral convergent strabismus; an inability of the eye to cross the midline when evaluating the horizontal physiological nystagmus; and an inability to retract the eyeball. Isolated lesions are rare, as for CN IV.

### Facial nerve - CN VII

Anatomy and function: CN VII provides motor function to the muscles of facial expression and sensory function (providing the sense of taste) to the rostral two-thirds of the tongue and palate. Its parasympathetic component innervates the lacrimal glands and the mandibular and sublingual salivary glands. Neurons innervating the muscles of facial expression are located in the facial nucleus in the rostral medulla oblongata. The axons pass through the internal acoustic meatus of the petrosal bone on the dorsal surface of the vestibulocochlear nerve and leave the skull through the stylomastoid foramen. The facial nerve courses through the middle ear before branches are distributed to the muscles of facial expression (ear, eyelids, nose, cheeks, lips) as well as the caudal portion of the digastric muscle. The parasympathetic fibres (which produce lacrimal gland secretion) leave the facial nerve as it courses through the middle ear.

Clinical evaluation: The motor function of CN VII is primarily assessed by observation of the face for symmetry (position of the ears and lip commissure on each side within the same plane, symmetry of the palpebral fissure), spontaneous blinking and movement of the nostrils. The facial nerve also provides the motor response (efferent part) of the following tests:

- Palpebral reflex (CN V and VII)
- Corneal reflex (CN V and VII)
- Menace response (CN II and VII)
- · Pinching of the face (CN V and VII).

The Schirmer tear test can evaluate the parasympathetic supply of the lacrimal gland associated with CN VII. Examining the mouth for a moist mucosa can subjectively assess salivation.

Clinical signs of dysfunction: Motor dysfunction of CN VII produces: ipsilateral drooping of and inability to move the ear and lip; widened palpebral fissure and absent spontaneous and provoked blinking; absent abduction of the nostril during inspiration; and deviation of the nose toward the normal side due to the unopposed muscle tone on the unaffected side (Figure 1.23) (see Chapter 11). With chronic denervation, the lips are retracted further than normal and the nostril is deviated to the affected side as a result of muscle fibrosis.

Facial spasm can also be seen, causing retraction of the lips and nostril to the affected side, and narrowing of the palpebral fissure on the affected side. This can be distinguished from chronic denervation by performing the palpebral test: in facial spasm the eye can blink.



Facial asymmetry with dropping of the ear, drooping of the lip and deviation of the nostril to the unaffected side in a 7-year-old male Labrador with acute idiopathic facial nerve paralysis (CN VII).

Unilateral involvement can be seen in the asymmetry of the ears, eyelids, lips and nose. Lesions of the individual branches of the facial nerve along their course produce paresis or paralysis of the specific muscles they innervate. Dysfunction of the parasympathetic supply of the lacrimal gland produces keratoconjunctivitis sicca. This is mainly seen with lesions of the facial nerve located between the medulla and the middle ear. Lesions distal to the facial canal in the temporal bone will not affect these parasympathetic neurons.

## Vestibulocochlear nerve - CN VIII

**Anatomy and function:** The vestibulocochlear nerve is involved in hearing and vestibular function (adaptation of position of the eye and body with respect to the position and movement of the head).

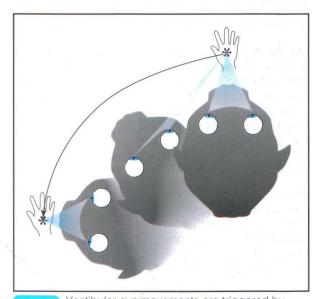
The vestibular system consists of special proprioreceptors within the petrous temporal bone (inner ear), the vestibular nerve, and four brainstem nuclei located in the rostral medulla oblongata on each side of the fourth ventricle (see Chapter 10). The receptor organs (saccule, utricle and semi-circular canals) detect the position and movement of the head. The neurons of the vestibular ganglia receive impulses from these receptors and project into the vestibular nuclei via the internal acoustic meatus, where this special proprioceptive information is integrated. The vestibular nuclei connect to the nuclei of the cranial nerves responsible for eye movement (CN III, IV, VI) via the medial longitudinal fasciculus. They also project to the ipsilateral extensor muscles of the limb via the vestibulospinal tract. Finally, these neurons project to the ipsilateral flocculonodular lobe of the cerebellum via the caudal cerebellar peduncles. Through these pathways, the vestibular system controls the position of the eyes, trunk and limbs depending on the position and movements of the head.

The hearing system involves the sensory receptor organ (organ of Corti) within the cochlea of the inner ear.

The neurons forming the cochlear branch of CN VIII have their cell bodies in the spiral ganglion of CN VIII. They receive impulses from the neuroepithelial hair cells of the organ of Corti, enter the brainstem and synapse with the cochlear nuclei. The auditory information is then transmitted to the contralateral medial geniculate nucleus of the diencephalon via the lateral lemniscus. From this nucleus, a third neuron projects via the auditory radiation to the contralateral auditory cortex.

Clinical evaluation: Observation of the animal's body and head posture at rest, and evaluation of its gait, can provide a lot of information about the vestibular function of CN VIII. This function can also be more specifically assessed by testing the vestibulo-ocular reflex (also known as physiological nystagmus). This type of nystagmus (also called 'jerk' nystagmus) is an involuntary rhythmic movement of the eyes, which typically presents with a slow phase in one direction and a guick phase in the other direction. It can occur in normal animals (physiological or vestibular nystagmus) or may be associated with an underlying abnormality (pathological nystagmus; see Chapter 10). The direction of the nystagmus is classically described by that of the fast-phase movement. A physiological nystagmus can be induced in normal individuals by lateral rotation of the head (Figure 1.24). This nystagmus stabilizes images on the retina during head movement. It is always observed in the plane of rotation of the head and consists of a slow phase in the direction opposite to that of the head rotation and a fast phase in the same direction as the head rotation. In the absence of any head movement, nystagmus should never be present in a normal animal.

The auditory function of CN VIII is difficult to assess clinically. The startle reaction consists of observing the animal's response to noise (e.g. handclap, whistle). Unilateral or partial deafness is virtually impossible to



Vestibular eye movements are triggered by movement of the head in a lateral direction. The eye movements are seen to be slower than the head movement but the eyes eventually return to the centre of the palpebral fissure.

detect using this test. The best assessment is the animal's response to noise when asleep: most owners can report whether they have to touch their animal in order to wake them. Electrophysiological assessment (such as the brainstem auditory evoked response test) (see Chapter 4) is necessary to confirm and assess the severity of the hearing loss.

Clinical signs of dysfunction: Vestibular dysfunction may result in any or all of the following clinical signs: head tilt; falling; leaning; rolling; circling; abnormal and/or positional nystagmus (Figure 1.25); positional strabismus (Figure 1.26); and asymmetrical ataxia (see Chapter 10). Clinical signs may be a result of lesions involving the receptor organs in the inner ear or the vestibular portion of CN VIII (e.g. peripheral vestibular dysfunction) or lesions involving the brainstem vestibular nuclei (e.g. central vestibular dysfunction). Less frequently, lesions affecting the caudal cerebellar peduncle, the fastigial nucleus or the flocculonodular lobes of the cerebellum can cause central vestibular dysfunction with a resulting paradoxical head tilt. Bilateral vestibular disease is characterized by head sway from side to side, loss of balance on both sides and symmetrical ataxia with a wide-based stance. A physiological nystagmus cannot be elicited.



1.25 Placing an animal in dorsal recumbency can help in detecting a positional nystagmus or strabismus by 'challenging' the vestibular system.



Ventrolateral positional strabismus in a Rottweiler with a central vestibular syndrome. This strabismus was visible only visible by placing the head in a certain position, indicating a sensory dysfunction (vestibular apparatus) rather than a motor one (CN III – oculomotor disorder).

The presence of spontaneous or positional jerk nystagmus indicates vestibular dysfunction but does not further localize the lesion to the peripheral or central vestibular system. Some exceptions are worth mentioning:

- Positional, spontaneous and physiological nystagmus are usually absent with bilateral lesions
- Vertical nystagmus and nystagmus that changes direction with different head positions are most commonly seen with central lesions.

## Glossopharyngeal and vagus nerves – CN IX and CN X

Anatomy and function: The glossopharyngeal and vagus nerves share sensory (solitary nucleus) and motor (nucleus ambiguus) nuclei. CN IX innervates the musculature of the pharynx and palatine structures. It provides sensory innervation to the caudal third of the tongue and pharyngeal mucosa (taste). Its parasympathetic component innervates the parotid and zygomatic salivary glands. CN X controls motor function of the larynx (recurrent laryngeal branch), pharynx and oesophagus (the cervical oesophagus is innervated by the pharyngeal and recurrent laryngeal branches, while the thoracic oesophagus is innervated by the vagal branches). It provides sensory function to the larynx, pharynx, and thoracic and abdominal viscera. Its parasympathetic component provides innervation to all thoracic and abdominal viscera, except those of the pelvic region.

Clinical evaluation: The pharyngeal (swallowing or gag) reflex can assess the function of CN IX and CN X. It is evaluated by applying external pressure to the hyoid bones to stimulate swallowing (Figure 1.27) or by stimulating the pharynx with a finger to elicit a gag reflex. It can also be evaluated by watching the animal



The swallowing reflex can be elicited by applying gentle pressure on the hyoid bones and thyroid cartilage.

eat or drink or by opening its mouth wide; the animal will usually close its mouth, swallow and lick its nose, allowing simultaneous evaluation of the tongue. The parasympathetic portion of CN X can be evaluated by testing the oculocardiac reflex. This is achieved by applying digital pressure to both eyeballs and observing simultaneously a reflex bradycardia (also mediated by CN V).

Clinical signs of dysfunction: CN IX dysfunction results in dysphagia, absent gag reflex and reduced pharyngeal tone. Animals frequently cough after drinking and swallow repeatedly because of an accumulation of saliva in their pharynx. CN X dysfunction results in dysphagia, inspiratory dyspnoea (due to laryngeal paralysis), voice changes (dysphonia) and regurgitation (due to megaoesophagus in the case of bilateral vagal disorder). The pharyngeal and oculocardiac reflexes are absent.

## Accessory nerve - CN XI

**Anatomy and function:** CN XI provides motor innervation to the trapezius and part of the sternocephalicus and brachiocephalicus muscles.

Clinical signs of dysfunction: Lesions of this nerve result in trapezius muscle atrophy. The neck may be deviated toward the affected side in chronic cases. Isolated lesions of the accessory nerve are an extremely rare finding.

## Hypoglossal nerve - CN XII

**Anatomy and function:** CN XII provides motor innervation to the muscles of the tongue. The nucleus is in the caudal medulla and can therefore be affected by high cervical lesions. This cranial nerve exits by the hypoglossal foramen.

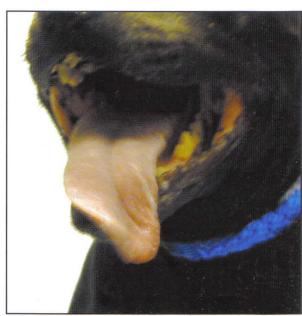
Clinical evaluation: CN XII function can be evaluated by inspecting the tongue for atrophy, asymmetry or deviation to one side. Manually stretching the tongue and observing a voluntary retraction assesses the tongue's tone. Applying food paste to the nose and observing the animal licking assesses the tongue's movement.

Clinical signs of dysfunction: Lesions affecting CN XII can result in problems with prehension, mastication and deglutition. With unilateral and recent lesions, the tongue tends to deviate toward the contralateral side (Figure 1.28). With unilateral and chronic lesions, the tongue protrudes toward the side of the lesion and atrophy is observed ipsilaterally. Muscle fasciculations may be obvious on the affected side in the denervated tongue.

## Postural reaction testing

## Anatomy and function

The sense of kinaesthesia is the awareness of the precise position and movements of the body and



1.28 Deviation and atrophy of the tongue caused by a left-sided hypoglossal nerve paralysis. (Courtesy of Simon Platt, Animal Health Trust)

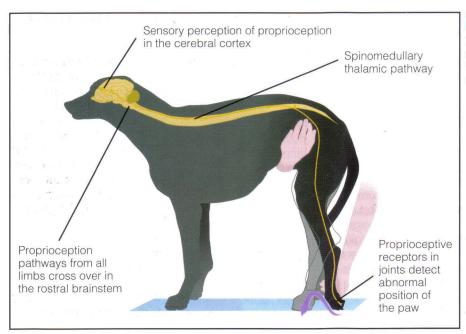
especially the limbs. Proprioceptors are specific receptors sensitive to these movements. They are located in the joint, tendon and muscles (general proprioception) as well as in the inner ear (special proprioception). The information collected by these receptors is transmitted to the cerebral cortex, where it is consciously perceived (conscious proprioception). This sensory function can be tested using the following postural reactions:

- Proprioceptive positioning (paw position or 'knuckling' response)
- · Hopping and hemi-walking
- · Visual or tactile placing response.

These responses are complex in their pathways but generally involve, in the afferent arc: a proprioceptive receptor; a peripheral sensory nerve; spinothalamic ascending pathways and the contralateral somatic sensory area of the cerebral cortex (integration centre); and, in the efferent arc: contralateral motor cortex; descending motor pathways within the brainstem and spinal cord (UMN); and peripheral motor nerve (LMN) and skeletal effector muscles (Figure 1.29).

The entire nervous system is needed to be able to perform postural reactions. Testing them is a very important tool for detecting subtle dysfunction and asymmetries and confirming that a neurological disease is present. Lesions affecting any of the above anatomical sensory and motor components could result in abnormal postural reactions. Although these reactions detect neurological dysfunction, they do not provide specific information for lesion localization.

In general, postural reactions remain normal in postsynaptic junctional and muscular diseases, as long as the animal has the strength to support its weight.



## 1.29

Proprioceptive positioning response in the pelvic limb. Note it is important to support the animal's bodyweight as shown.

## Clinical evaluation

**Proprioceptive positioning:** This test is designed to evaluate the conscious awareness of the limb position and its movement in space. It is the most commonly used postural reaction test in the dog. It is particularly difficult to perform in cats, which resent having their feet handled during proprioceptive positioning.

Conscious proprioception is evaluated by placing the paw in an abnormal position (turned over so that the dorsal surface is in contact with the ground) and determining how quickly the animal corrects the paw position (Figure 1.30). When performing this test, the animal should be standing squarely on all four limbs, and it is fundamental to support the majority of the animal's weight in order to improve test sensitivity. Failure to do so causes flexion of the limb, which results in the stimulation of many proprioceptors within the different flexed joints. Supporting their weight is also helpful for animals that are reluctant to bear weight because of a painful limb (as seen with some orthopaedic diseases). The test should be repeated until the examiner is confident with the result. Conscious proprioceptive deficits are seen in many neurological conditions and are sensitive but non-specific indicators of nervous system disease.

The 'sliding paper' test is another proprioceptive positioning test. A piece of paper is placed under the weight-bearing foot of the animal and slowly pulled laterally. A normal animal will pick up the limb and replace it in the correct position. This sliding paper test mainly evaluates conscious proprioception in the proximal part of the limb.

**Hopping reaction:** This test is the preferred postural reaction test in cats. It can be particularly difficult to perform in large breeds of dog. The hopping reaction is tested by holding the patient so that the majority of its weight is placed on one limb while the animal is moved laterally (Figure 1.31). Normal animals hop on the tested



Changing paw position evaluates the conscious awareness of the limb position by the animal (conscious proprioceptive function). This cortically mediated response is elicited by gently placing the dorsal surface of the animal's foot on the floor. Care should be taken to support the animal's weight. The animal should immediately replace its foot in a normal position.



response is tested in the left thoracic limb of this dog. The right thoracic limb is held off the ground and the hind end is supported to put the majority of weight on the left thoracic limb. The dog is then pushed to the left.

limb to accommodate a new body position as their centre of gravity is displaced laterally. An equal response should be seen on both sides. Subtle ataxia or weakness of one limb may be detected. Animals with severe orthopaedic disease will have difficulty performing this test unless their weight is supported adequately.

Placing response: Visual placing and tactile placing are, in principle, much more complex postural reaction tests. They are mainly used when proprioceptive positioning or hopping reactions do not confirm a disorder. Visual placing can also be useful in assessing visual function in an animal where the menace response or obstacle course testing is difficult to interpret. Tactile placing is tested with the animal's eyes covered. The animal is lifted and the distal part of the thoracic limb is brought in contact with the edge of a table. When the dorsal surface of the paw makes contact with the edge of the surface, the animal should immediately place its foot on the surface. Visual placing is tested by allowing the animal to see the table surface. Normal animals will reach for the surface before the paw touches the table.

Hemi-walking and wheelbarrowing: These are also more complex postural reaction tests. Wheelbarrowing tests the thoracic limbs: the animal's pelvic limbs are lifted off the ground by supporting the animal under the abdomen and forcing it to walk forwards. This test highlights subtle thoracic limb weakness and ataxia. Subtle vestibular dysfunction can be detected by extending the animal's head and neck while testing. Hemiwalking tests the ability of the animal to walk on the thoracic and pelvic limbs on one side while holding the limbs on the other side. The animal should be pushed away from the side on which its limbs are supported and the speed and coordination of the movements assessed. This is best performed on a non-slip surface.

## Spinal reflexes; muscle tone and size

Spinal reflex evaluation is performed to classify the neurological disorder as being of LMN or UMN type (Figure 1.32). This allows the examiner to localize the lesion to specific spinal cord segments or peripheral nerves.

## Differentiation between lower and upper motor neuron lesions

Lower motor neuron: An LMN is an efferent neuron connecting the CNS to an effector organ. Its cell body lies within the ventral horn of the spinal cord grey matter or within the cranial nerve nucleus of the brainstem. Its axon leaves the CNS as the ventral nerve roots, becoming a spinal nerve and then a peripheral nerve, before it synapses with an effector organ (muscle or gland). The LMN is the last neuron in the chain of neurons that produce muscular contraction (final common pathway to the effector). If LMNs are damaged, the following clinical signs are characteristically found:

- Flaccid paresis and/or paralysis
- Reduced or absent reflexes (hyporeflexia or areflexia)
- Reduced or absent muscle tone (hypotonia or atonia)
- Early and severe muscle atrophy (neurogenic atrophy).

The CNS is arranged in a segmental manner. Each spinal cord segment innervates a specific muscle or group of muscles (called a myotome). Identification of segmental LMN signs allows accurate clinical neurolocalization to a peripheral nerve, a nerve root or a motor neuron within the spinal cord or the brainstem.

Upper motor neuron: UMN refers to any efferent neuron originating in the brain and synapsing indirectly (via an interneuron) with an LMN to modulate its activity. The UMN is responsible for the initiation and maintenance of normal movements and for the maintenance of tone in the extensor muscles to support the body against gravity. It also has an inhibitory effect on myotatic reflexes. Its cell body lies within the cerebral cortex, basal nuclei or brainstem.

Lesions of the UMN system typically result in loss of motor function and the release of the inhibitory effect (disinhibition) that the UMN system has on LMNs located caudal to the level of the injury. This disinhibition is usually more apparent in the extensor muscles.

Criteria	Lower motor neuron paresis	Upper motor neuron paresis
Posture	Difficulty in supporting weight Crouched stance as a result of overflexion of the joints	Often normal (unless the animal is paralysed) Abnormal limb position (knuckling, abducted, adducted or crossed over)
Gait	Short strides Tendency to collapse	Stiff and ataxic strides  Delayed protraction
Motor function	Flaccid paresis/paralysis	Spastic paresis/paralysis
Segmental reflexes	Decreased to absent	Normal to increased
Resting muscle tone	Decreased to absent	Normal to increased
Passive limb flexion and extension	Decreased resistance	Slight resistance
Muscle atrophy	Early and severe neurogenic atrophy	Late and mild disuse atrophy

Criteria for differentiation between lower motor neuron and upper motor neuron paresis.

Clinically, the result is:

- · Spastic paresis and/or paralysis
- Normal to increased reflex activity (hyperreflexia)
- Increased extensor muscle tone (hypertonia) manifested as a resistance to passive manipulation of the limbs
- Chronic mild to moderate muscle atrophy (disuse atrophy).

Unlike LMN signs, identification of UMN signs does not allow accurate clinical neurolocalization to a specific spinal cord segment or brainstem nucleus.

### Regions of the spinal cord

Functionally the spinal cord can be divided into four regions:

- Cranial cervical (C1-C5)
- Cervicothoracic (C6–T2)
- Thoracolumbar (T3–L3)
- Lumbosacral (L4-S3).

LMN cell bodies are located within the grey matter of the cervicothoracic intumescence (segments C6–T2) for the thoracic limbs and the lumbosacral intumescence (segments L4–S3) for the pelvic limbs. Lesions at these levels result in LMN signs in the corresponding limb(s). Spinal reflexes and muscle tone are evaluated with the animal placed in lateral recumbency. In paretic animals, each paretic limb is evaluated with the aim of categorizing it as an LMN or UMN paresis. This assessment should allow localization of the lesion to one of the four functional regions of the spinal cord, to the brain or to the peripheral nervous system (Figure 1.33).

Site of the lesion	Thoracic limbs	Pelvic limbs
Brain	UMN	UMN
C1-C5	UMN	UMN
C6-T2	LMN	UMN
T3-L3	Normal	UMN
L4-S3	Normal	LMN
Polyradiculopathy Polyneuropathy	LMN	LMN

1.33 Neurolocalization based on the presence of upper motor neuron (UMN) or lower motor neuron (LMN) paresis.

## Evaluation of the thoracic limbs

Withdrawal (flexor) reflex: In the thoracic limb, this reflex evaluates the integrity of spinal cord segments C6–T2 (and associated nerve roots) as well as the brachial plexus and peripheral nerves (axillary, musculocutaneous, median and ulnar nerves). This reflex is performed with the animal in lateral recumbency. A noxious stimulus is applied to the tested limb by pinching the nail bed or digit with the fingers or a haemostat. This stimulus causes a reflex contraction

of the flexor muscles and withdrawal of the tested limb. Sensory input is through the median, ulnar and radial nerves, and motor output is through C6-T2 spinal cord segments and nerve roots of the axillary. musculocutaneous, median and ulnar nerves. If this withdrawal reflex is absent, individual toes should be tested to detect whether specific nerve deficits are present. When testing the flexor reflex, the contralateral limb should be observed for extension (crossed-extensor reflex), indicating a UMN lesion cranial to the C6 spinal cord segment. It should be stressed that the withdrawal reflex in the thoracic or pelvic limbs does not depend on the animal's conscious perception of noxious stimuli (nociceptive function). The withdrawal reflex is a segmental spinal cord reflex that only depends on the function of the local spinal cord segments.

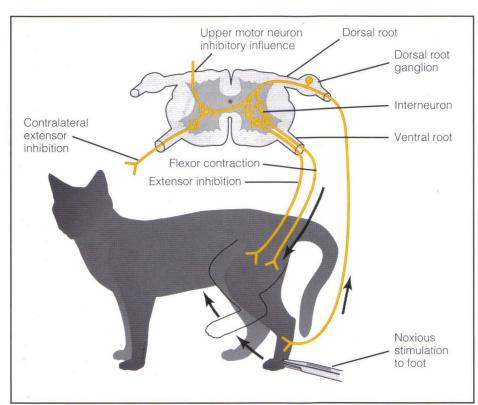
Extensor carpi radialis reflex: This is tested by striking the extensor carpi radialis muscle belly with a reflex hammer at the proximal region of the antebrachium while the carpus is slightly flexed (Figure 1.34). The desired reaction is a slight extension of the carpus. This reflex evaluates the integrity of spinal cord segments C7–T2 and associated nerve roots as well as the radial nerve.



1.34

Extensor carpi radialis reflex is tested by hitting the proximal region of the antebrachium and observing a slight extension of the carpus.

Biceps brachii and triceps reflexes: These are less reliable reflexes than the withdrawal and extensor carpi radialis reflexes and are not always present in the normal animal. A finger is placed over the distal end of the biceps brachii and brachialis muscle at the level of the elbow. Striking the finger with a reflex hammer can elicit the biceps reflex; a normal reaction is the flexion of the elbow or at least the contraction of the biceps muscle. The triceps reflex is elicited by striking the triceps tendon proximal to its insertion on the olecranon. The desired reaction is an extension of the elbow or carpus. These reflexes evaluate the integrity of C6-C8 (biceps) and C7-T1 (triceps) spinal cord segments and associated nerve roots, as well as the musculocutaneous (biceps) and radial (triceps) nerves.



Withdrawal (flexor) 1.35 reflex. When a noxious stimulus is applied to a digit, the limb should be withdrawn towards the body. Sensory input enters the spinal cord through the dorsal root to activate ipsilateral flexor motor neurons via interneurons and simultaneously inhibit the antagonistic extensor muscles. Contralateral stimulation of extensor muscles is inhibited by the descending upper motor neuron influence on the contralateral lower motor neurons

## Evaluation of the pelvic limbs

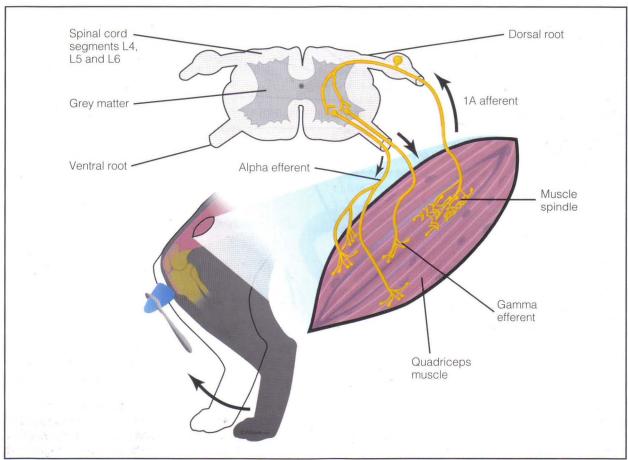
Withdrawal (flexor) reflex: In the pelvic limb, this reflex evaluates the integrity of spinal cord segments L4-S2 (and associated nerve roots) as well as the femoral and sciatic nerves. A normal reflex constitutes flexion of the hip (femoral nerve function), stifle and hock (sciatic nerve function) (Figures 1.35 and 1.36). Sensory input is through the tibial and peroneal branches of the sciatic nerve (lateral, dorsal and ventral aspect of the foot) and the saphenous branch of the femoral nerve (medial aspect of the foot including the second digit). Motor output is through L4-S2 spinal cord segments and nerve roots, femoral nerves, sciatic nerves and associated tibial and peroneal branches. The hock must be extended in order to evaluate sciatic function (i.e. hock flexion). A crossed-extensor reflex in the pelvic limb indicates a UMN lesion cranial to the L4 spinal cord segment.

Patellar reflex: This monosynaptic myotatic (or stretch) reflex involves the following anatomical components: muscle spindles (fusus neuromuscularis sensitive to stretch); sensory neuron; spinal cord segment; efferent motor neuron; and muscle effector (Figure 1.37). This reflex evaluates the integrity of spinal cord segments L4–L6 (and associated nerve roots) as well as the femoral nerve. It is performed when the animal is in lateral recumbency, with the stifle slightly flexed and the tested limb supported by placing one hand under the thigh. Striking the patellar tendon with a reflex hammer induces extension of the limb due to a reflex contraction of the quadriceps femoris muscle (Figure 1.38). A weak or absent reflex indicates a lesion of the L4–L6 spinal cord segments or the femoral nerve. A similarly weak or



1.36 A normal withdrawal (flexor) reflex in the pelvic limb implies flexion of the hock, stifle and hip. While the withdrawal is evoked, the contralateral limb should be observed for reflex extension (crossed-extensor reflex).

absent reflex can occasionally be seen with previous stifle disease or as an age-related change. A lesion cranial to the L4 spinal cord segment can cause a normal or exaggerated reflex. In the absence of other neurological deficits, an exaggerated patellar reflex means little and can be observed in an excited or nervous animal. Finally, the patellar reflex can appear hyperreflexic with a sciatic nerve or L6–S2 spinal cord segment lesion. This pseudo-hyperreflexia is a result of decreased tone in the muscles that flex the stifle and normally counteract stifle extension during the patellar reflex.



Myotatic (stretch) reflex. Striking the patellar ligament stretches (indirectly) the muscle spindles within the quadriceps muscle, which activates the 1A afferent fibres. The sensory fibres synapse directly on to motor neurons to the quadriceps femoris.



1.38 The patellar reflex is elicited by hitting the patellar ligament and observing a reflex extension of the stifle joint.



tibial reflex is elicited by hitting the proximal part of the cranial tibial muscle and observing a reflex flexion of the tarsus.

Cranial tibial and gastrocnemius reflexes: These are less reliable than the patellar reflex. The cranial tibial reflex is elicited by striking the proximal part of the cranial tibial muscle with a reflex hammer and observing for flexion of the tarsus (Figure 1.39). The gastrocnemius reflex is elicited by placing the finger over the gastrocnemius muscle and striking it with a hammer. The normal reaction is extension of the hock. These reflexes evaluate the integrity of the spinal cord segments L6–S1 (cranial tibial)

and L7-S1 (gastrocnemius) and associated nerve roots, as well as the integrity of the peroneal (cranial tibial) and the tibial (gastrocnemius) peripheral nerves.

## Evaluation of the tail and anus

Examination of the tail and anus are an essential part of the evaluation of the spinal reflexes that is often overlooked by the clinician. Bladder function and evaluation are described in Chapter 18.

**Perineal reflex:** Stimulation of the perineum with a haemostat results in contraction of the anal sphincter and flexion of the tail (Figure 1.40). This reflex tests the integrity of caudal nerves of the tail, the pudendal nerve, spinal cord segments S1–Cd5 and associated nerve roots.



The perineal reflex consists of clamping the tail and contraction of the anal sphincter as a result of stimulation of the perineum.

## Sensory evaluation

Apart from conscious proprioception (see above), evaluation of the sensory system in animals largely depends on tests for pain perception (nociception). Touch, pressure and temperature sensation are extremely difficult to assess objectively in animals.

- Anaesthesia refers to a complete loss of all forms of sensation.
- Hypoaesthesia refers to a diminution of sensation.
- Hyperaesthesia refers to increased sensitivity to a normal level of stimulation.
- Analgesia, hypoalgesia and hyperalgesia refer to loss, impairment and increased sensitivity to pain, respectively.

The purpose of testing pain perception is to detect and map out any areas of sensory loss. Assessment of pain sensation requires a noxious stimulus and evaluation of the animal's response.

## **Cutaneous sensory testing**

A dermatome is an area of skin that corresponds to a specific nerve root and spinal cord segment. Areas of decreased or absent cutaneous pain perception may aid in identification of specific peripheral nerves, nerve roots and spinal cord segments involved in the disease process. Dermatomal mapping of clinical use in the dog or cat is summarized in Figure 1.41. Cutaneous sensation is evaluated by pinching the skin with a haemostat. The response elicited may be a behavioural response or a withdrawal reflex. The presence of either response indicates functional integrity of the particular sensory nerve tested. Conscious perception of the stimulus (behavioural response such as a turning of the head or vocalization) indicates that the cutaneous nerve being

Nerve	Spinal cord segment	Cutaneous sensory distribution
Musculocutaneous	C6, C7, C8	Medial antebrachium
Radial	C7, C8, T1, T2	Cranial aspect of the antebrachium and foot except the fifth digit
Median and ulnar	C8, T1, T2	Caudal aspect of the antebrachium and foot (including fifth digit)
Femoral	L3, L4, L5, L6	Medial aspect of the limb and first digit (saphenous branch)
Sciatic: Peroneal branch Tibial branch	L6, L7, S1, S2	Craniolateral aspect of limb distal to stifle Caudal aspect of limb distal to stifle

1.41 Dermatomal mapping of clinical use in dogs.

tested, the afferent nociceptive pathways within the spinal cord and brain, and the appropriate portions of the cerebral cortex are functional. A withdrawal reflex simply indicates that the cutaneous nerve tested, the spinal cord segments and efferent motor neuron of the withdrawal reflex are functional. If an area of diminished or absent pain sensation is encountered, its boundaries should be demarcated to see whether it has a segmental or peripheral nerve distribution and whether it is absent below a certain level of the trunk.

## Evaluation of the cutaneous trunci (panniculus) reflex

This reflex is elicited by pinching the skin of the dorsal trunk between vertebral level T2 and L4–L5, and observing a contraction of the cutaneous trunci muscles bilaterally, producing a twitch of the overlying skin (Figure 1.42). This reflex is present in the thoracolum-



The cutaneous trunci (panniculus) reflex is activated by pinching the skin over the lumbar spine with forceps. It should be tested from caudal to cranial on each side of the spine, starting at the level of the wings of the ilium. Bilateral contraction of the cutaneous trunci muscle indicates a normal reflex. In the absence of such muscle contraction, the point of skin stimulation should be moved cranially until a normal reflex is observed.

bar region and is absent in the neck and sacral region. From the dermatome tested, the sensory nerve from the skin enters the spinal cord at the level of the segments corresponding to that dermatome (approximately two vertebrae cranial to the level tested). Afferent sensory information ascends the spinal cord and synapses bilaterally at the C8–T1 spinal cord segments with the motor neurons of the lateral thoracic nerve, which courses through the brachial plexus and innervates the cutaneous trunci muscle. The cutaneous trunci reflex can be decreased or lost caudal to a lesion anywhere in this pathway.

Testing is started at the level of the ilial wings: if the reflex is present at this level the entire pathway is intact and further testing is not necessary. With spinal cord lesions, this reflex is lost caudal to the spinal cord segment affected, indicating the presence of a transverse myelopathy. Pinching the skin cranial to the lesion results in a normal reflex, while stimulation of the skin caudal to the lesion does not elicit any reflex. Such findings help to further localize lesions between T3 and L3. This reflex can also be lost ipsilaterally (with a normal contralateral reflex) with disease affecting the brachial plexus (and hence the motor lateral thoracic nerve) regardless of the level at which the skin is stimulated. In the absence of other neurological deficits, a lack of the cutaneous trunci reflex means very little.

## Deep pain perception

For pain to be perceived consciously, the sensory component of the peripheral nerves and their spinal cord segments, the spinal cord and brainstem and the related thalamocortex system must all be intact and functional. Pain can often be elicited by heavy pressure to the bones of the digits of a thoracic or pelvic limb with a haemostat, even when cutaneous pain sensation is diminished or lost. This has been termed deep pain sensation. The pathways that carry deep pain sensation are located deep in the spinal cord white matter and project to both sides of the spinal cord, forming a multisynaptic bilateral network. Therefore, only a severe bilateral spinal cord lesion impairs the sensation of deep pain. For this reason, testing of deep pain perception (Figure 1.43) is a useful prognostic indicator in cases of spinal cord disease. This



Deep pain perception is tested by pinching the digits with the fingers or with haemostats. Only a behavioural response to this noxious stimulus (turning of the head, vocalization, attempt to bite) indicates conscious pain perception. If no response is elicited when using fingers, the test should be repeated with haemostats to ensure that the response is absent.

conscious pain perception must be assessed in all four limbs, the tail and the perineal region. The expected reaction is a behavioural response such as turning the head, trying to bite or vocalization (Figure 1.43). The animal is placed on its side, ideally with a second person talking to it or stroking it to distract its attention. A gentle squeeze is applied initially to the digits to elicit the withdrawal reflex. If the animal does not manifest any behavioural response following a gentle squeeze, heavy pressure is then applied.

Withdrawal of the limb is only the flexor reflex and should not be taken as evidence of pain sensation.

## **Palpation**

Palpation and manipulation to detect painful areas and/or restricted movement (Figures 1.44 and 1.45) is usually performed last to avoid losing the cooperation of the patient.

**Head:** The head must be palpated to detect any asymmetry, focus of pain or persistence of the bregmatic fontanelles.

**Spine:** Palpation of the spine is started by applying gentle downward pressure on the spinous process and then along the transverse processes. The degree of



The spine can be palpated while the animal is standing or recumbent. Spinal hyperaesthesia is detected by applying gentle pressure on the dorsal spinous processes and transverse processes of the spine. Simultaneous palpation of the abdomen can help to detect the focus of hyperpathia.



Gently manipulating the neck in dorsal, lateral and ventral flexion can help to detect pain and a reduced range of movement.

pressure to be applied should be increased progressively. The presence of spinal hyperaesthesia or deformity should be noted.

Limbs: Palpation of the limbs is indicated to evaluate the animal for musculoskeletal conditions that could mimic a neurological disorder. The joints should be palpated carefully for evidence of swelling, pain or instability. Palpation of the muscular system can help to detect focal muscle atrophy. Such findings could indicate disease in the spinal cord segment, nerve root or peripheral nerve that innervates that muscle (see LMN signs) or could be related to disuse atrophy associated with an orthopaedic condition.

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## Lesion localization and differential diagnosis

## **Laurent Garosi**

## Introduction

Precise localization of the causative disorder within the nervous system (anatomical diagnosis) and an understanding of the suspected disease processes (differential diagnosis) are the keys to an accurate neurological diagnosis.

The past decade has seen a dramatic increase in the availability of sophisticated neurodiagnostic tests (e.g. electrodiagnosis, computed tomography, magnetic resonance imaging). The advantages of using such technology are undeniable when considering diagnostic capability and progress in the understanding of complex neurological problems. Unfortunately, despite their relatively high sensitivity, these diagnostic tests often lack specificity in identifying the exact nature of the disease process. The clinician must therefore still rely on clinical acumen to choose and interpret the appropriate diagnostic test. Accurate determination of the neurolocalization is essential in the choice and interpretation of any diagnostic tests. Furthermore, valuable information can be obtained from the suspected lesion distribution to establish a differential diagnosis list (see below).

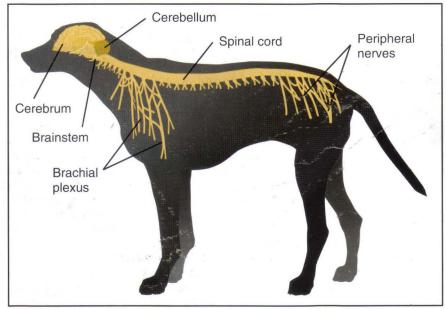
## Functional neuroanatomy and anatomical diagnosis

Based on the animal's history and a neurological examination, the clinician can determine whether the animal suffers from a neurological disease. If so, attempts should be made to localize the lesion within the nervous system (anatomical diagnosis) prior to establishing a differential diagnosis list.

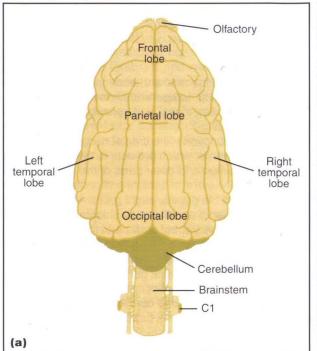
The major anatomical regions of the nervous system include intracranial and extracranial structures (Figures 2.1 and 2.2).

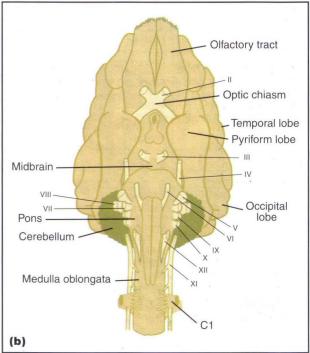
## Intracranial structures

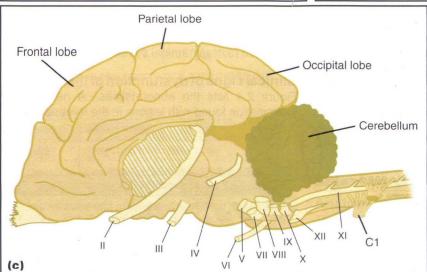
- Forebrain
  - Cerebrum also called telencephalon
  - Diencephalon which includes thalamus and hypothalamus
- Brainstem
  - Midbrain also called mesencephalon
  - Pons also çalled metencephalon
  - Medulla oblongata also called myelencephalon
- Cerebellum also called dorsal metencephalon.



General overview of the topographical anatomy of the central and peripheral nervous system. This overview can be seen throughout the Manual, highlighting the specific section(s) of the nervous system relevant to the particular clinical signs under discussion.







The brain. (a) Dorsal view, showing the lobes of the cerebral hemispheres. (b) Ventral view. (c) Lateral view. C1 = cervical 1 segment of spinal cord. Cranial nerves: I = olfactory; II = optic; III = oculomotor; IV = trochlear; V = trigeminal; VI = abducent; VII = facial; VIII = vestibulocochlear; IX = glossopharyngeal; X = vagus; XI = accessory; XII = hypoglossal.

## **Extracranial structures**

- Spinal cord
  - C1-C5 spinal cord segments
  - C6–T2 spinal cord segments (cervicothoracic intumescence)
  - T3-L3 spinal cord segments
  - L4–S3 spinal cord segments (lumbosacral intumescence)
- Peripheral nervous system
  - Peripheral nerve
  - Neuromuscular junction
  - Muscle.

A basic knowledge of the function of each of these anatomical regions is essential in the interpretation of neurological examination findings. The neurological examination aims to test the integrity of the various components of the nervous system and to

detect any functional deficits. Normal results are as important as abnormal ones in establishing the anatomical diagnosis.

The interpretation of the neurological evaluation should begin by making a list of the abnormal results collected from the history and examination. Each of these abnormal findings should then be correlated to a specific region or to specific pathways within the peripheral and/or central nervous system (Figure 2.3). An attempt should always be made to explain all the abnormal findings by a single lesion within one of the regions of the nervous system noted above. Lesions within these regions of the nervous system result in predictable and specific neurological signs. It should be noted that in localizing a lesion, it is not necessary that all of the clinical signs referable to one location are present. If a single lesion cannot explain all the listed abnormal findings, the anatomical diagnosis is considered as multifocal or diffuse.

Clinical signs	Neurolocalization
Seizures [7]	Forebrain
Narcolepsy-cataplexy [17]	Diencephalon
Hemi-neglect syndrome [8]	Forebrain
Abnormal behaviour [8]	Forebrain
Visual dysfunction [9]	Eye, optic nerve, optic chiasm, forebrain
Head pressing [8]	Forebrain
Circling: With loss of balance [10] Without loss of balance [8]	Vestibular apparatus Forebrain
Head tilt, nystagmus, falling, rolling [10]	Vestibular apparatus
Strabismus [9]	Vestibular apparatus CN III, IV, VI
Depression, stupor, coma [8]	Brainstem or forebrain
Abnormal prehension [11]	CN V, XII, caudal brainstem
Dysphagia [11]	CN IX, X, caudal brainstem
Dropped jaw [11]	Bilateral CN V
Paralysis of eyelid, lip, nostril and/or ear [11]	CN VII
Megaoesophagus [11]	CN X
Laryngeal paralysis [11]	CN X
Tongue paralysis [11]	CN XII
Deafness [11]	Auditory apparatus

Examples of clinical signs and localization of the disorder causing them. The numbers in square brackets denote the chapters in this Manual where these conditions are discussed in detail.

CN = cranial nerve.

## **Forebrain**

## Anatomy and function

The forebrain is the area of the brain located rostral to the tentorium cerebelli (supratentorial region). It includes the cerebrum or telencephalon (cerebral cortex – grey matter; cerebral white matter; basal nuclei) and diencephalon (divided into thalamus, subthalamus, metathalamus and hypothalamus).

## Cerebrum

The cerebral cortex is important for behaviour, vision, hearing, fine motor activity and conscious perception of touch, pain (nociception), temperature and body position (proprioception).

The cerebral white matter mainly conveys ascending and descending sensory and motor activities. The basal nuclei are involved in muscle tone, and initiation and control of voluntary motor activity.

## Diencephalon

The diencephalon is the chief sensory-integrating system of the central nervous system (CNS). It is responsible for:

- Control of autonomic and endocrine functions (appetite, thirst, temperature, electrolyte and water balance), sleep, and consciousness or wakefulness
- Olfactory function via cranial nerve (CN) I, the olfactory nerve, which projects to the hypothalamus and other parts of the limbic system
- Vision and the pupillary light reflex via CN II, the optic nerve and the optic chiasm, which are located on the ventral surface of the hypothalamus
- A visual (via the lateral geniculate nucleus), auditory (via the medial geniculate nucleus), nociceptive and proprioceptive sensory relay system to the cerebral cortex
- Emotional behavioural patterns via connections with the limbic system.

The cell bodies of upper motor neurons (UMNs) are located in the motor cortex (pyramidal system) and the diencephalon, as well as motor centres of the brainstem (extrapyramidal system).

## Clinical signs of dysfunction of the forebrain

Figure 2.4 lists the abnormalities on neurological examination found with lesions in the forebrain.

Function	Abnormalities
Mental status	Altered mental status (depression/delirium/ dementia/stupor/coma) Behavioural changes
Cranial nerves	Contralateral blindness and decreased/absent menace reaction with normal pupillary light reflex
Posture/gait	Normal gait Abnormal movements and posture: pleurothotonus (body turn towards lesion), head turn, head pressing, pacing, wandering aimlessly and/or circling (usually ipsilateral)
Postural reactions	Postural reaction deficits in contralateral limbs
Spinal reflexes	Unaltered to increased in contralateral limbs
Muscle tone	Unaltered to increased in contralateral limbs
Sensation	Facial hypoalgesia Hypoaesthesia to contralateral half of body
Other findings	Seizures Hemi-neglect syndrome (see Chapter 8) Rarely, narcolepsy-cataplexy (see Chapter 17) Rarely, movement disorders such as dyskinesias (see Chapter 12)

Clinical signs caused by lesions in the forebrain.

## **Brainstem**

## Anatomy and function

Embryologically, the brainstem consists of all of the brain apart from the forebrain and cerebellum. It includes the midbrain (mesencephalon), the pons (metencephalon), the medulla oblongata (myelencephalon) and the cerebellar peduncles. The brainstem contains the regulatory centres for consciousness (ascending reticular activating system), the cardiovascular system and breathing (medullary reticular formation). It links the cerebral cortex to the spinal cord through ascending sensory and descending motor pathways, via what are often known as the 'long tracts'. Finally, it has ten pairs of cranial nerves (III to XII), that are involved in a variety of motor and sensory functions (see Chapter 1) including equilibrium and hearing.

## Clinical signs of dysfunction in the brainstem

Figure 2.5 lists the abnormalities on neurological examination found with lesions in the brainstem. The typical order of appearance of signs with progressive brainstem disease is:

- 1. Cranial nerve deficits
- 2. Proprioceptive deficits
- 3. Hemi/tetraparesis
- 4. Stupor/coma
- Abnormalities in respiratory and cardiovascular function.

Function	Abnormalities	
Mental status	Altered (depression/stupor/coma)	
Cranial nerves	Cranial nerve abnormalities (CN III to XII)	
Posture/gait	Paresis/paralysis of all four limbs (tetraparesis/ plegia) or of ipsilateral thoracic and pelvic limbs (hemiparesis/plegia); possibly opisthotonus; possibly decerebrate rigidity	
Postural reactions	Postural reaction deficits in all four limbs or in ipsilateral thoracic and pelvic limbs	
Spinal reflexes	Normal to increased spinal reflexes in all four limbs or in ipsilateral thoracic and pelvic limbs	
Muscle tone	Normal to increased tone in all four limbs or in ipsilateral thoracic and pelvic limbs	
Sensation	Unaltered, but can have cervical hyperaesthesia	
Other findings	Respiratory and cardiac abnormalities	

2.5

Clinical signs caused by lesions in the brainstem.

## Cerebellum (dorsal metencephalon)

## Anatomy and function

The cerebellum controls the rate, range and force of movements, without actually initiating motor activity.

The cerebellum coordinates muscle activity and 'smooths' movements induced by the UMNs. Because of its close association with the brainstem vestibular nuclei, it also functions in the maintenance of equilibrium and the regulation of muscle tone when the body is at rest or during motion. Finally, the cerebellum normally has an inhibitory influence on urination.

## Clinical signs of dysfunction of the cerebellum

Figure 2.6 lists the abnormalities on neurological examination found in patients with cerebellar disease.

Function	Abnormalities
Mental status	Unaltered
Cranial nerves	Ipsilateral menace deficit with normal vision and normal facial motor function Possibly vestibular signs Possibly anisocoria
Posture/gait	Intention tremors of head and eye Hypermetria with preservation of strength Truncal ataxia Broad-based stance Possibly decerebellate rigidity
Postural reactions	Delayed initiation and then (exaggerated) dysmetric response
Spinal reflexes	Unaltered
Muscle tone/mass	Normal to increased
Sensation	Unaltered Control of the Control of
Other findings	Possibly increased frequency of urination

2.6

Clinical signs caused by lesions in the cerebellum.

## Spinal cord

## Anatomy and function

The spinal cord lies within the vertebral canal. It arises at the level of the foramen magnum and extends up to the level of the sixth lumbar vertebra in most dogs and the seventh lumbar vertebrae in cats, where it tapers to form the conus medullaris. The spinal cord is composed of central grey matter and peripheral white matter. The diameter of the spinal cord is not constant throughout its length. In the caudal part of the cervical region and the lumbar region it widens to form the cervical and lumbar intumescences, respectively, from which the lower motor neurons (LMNs) to the thoracic and pelvic limbs arise.

### **Grey matter**

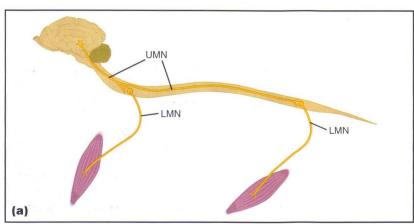
The spinal cord is composed of a central core of grey matter containing cell bodies of sensory neurons, interneurons and LMNs (Figure 2.7). The cell bodies of the efferent neurons are present in the ventral grey columns (somatic motor neurons responsible for innervation of striated muscles) and lateral grey columns (cell bodies of preganglionic sympathetic neurons in the thoracic and lumbar segments and preganglionic parasympathetic neurons in the sacral segments). The cell bodies of afferent (sensory) neurons are present in the dorsal root ganglions.

# Chapter 2 Lesion localization and differential diagnosis

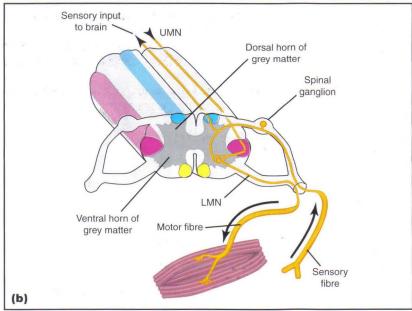
## White matter

The outer portion of the spinal cord is composed of white matter divided into three columns or funiculi (Figure 2.8):

- The dorsal funiculus consists essentially of ascending tracts mainly involved in proprioception
- The lateral funiculus contains both ascending (proprioception, touch, pressure, temperature and pain pathways) and descending (motor pathways) tracts
- The ventral funiculus contains only descending motor tracts.



2.7 The spinal cord. (a) Lateral view of the whole cord, showing a representative upper and lower motor neurons. (b) Cross-section showing grey matter and spinal ganglia. LMN = lower motor neuron; UMN = upper motor neuron.



Spinocuneocerebellar

Dorsal spinocerebellar

Ventral spinocerebellar

Ventral spinocerebellar

Spinothalamic

Spinoreticular

Spinoreticular

Sensory

tracts

Motor

tracts

2.8 Cross-section through the spinal cord, showing sensory and motor tracts.

# Segmentation

A spinal cord segment is defined as a portion of the spinal cord that gives rise to one pair of spinal nerves.

There are 8 cervical, 13 thoracic, 7 lumbar, 3 sacral and at least 2 caudal spinal cord segments in the dog and cat. Some spinal cord segments lie in the vertebra of the same annotation, while others lie cranial to the corresponding vertebra and their spinal nerves course caudally in the vertebral canal to exit at the correct intervertebral foramen (Figure 2.9).

Spinal cord segments and their locations relative to vertebral levels in the dog. With the exception of the first one or two cervical segments and segments L1 and L2, most spinal cord segments are positioned in the vertebral canal cranial to the vertebra of the same number. This disparity between the location of the spinal cord segments and their respective vertebrae is a result of the extra number of spinal cord segments in the cervical region (8 segments for 7 vertebrae) and the differential growth of skeletal and neural structures during embryological development. The cervical intumescence (C6-T2) lies within vertebrae C5-T1 and the lumbar intumescence (L4-S3) lies within vertebrae L3-L6. The spinal cord usually ends in L6-L7. The C1 spinal nerves exit through the lateral foramina in the C1 vertebra. The other cervical spinal nerves exit the vertebral canal cranial to the vertebrae of the same annotation, except the C8 nerves which exit between C7 and T1. All the other spinal nerves exit behind the samenamed vertebrae.

Spinal lesion localization refers to the spinal cord segments rather than the vertebral bodies.

Innervation in the body is organized in a segmental pattern. Each cutaneous region of the body (dermatome) and group of muscle fibres (myotome) is innervated by one spinal cord segment.

Functionally, the spinal cord can be divided into four regions:

- Cranial cervical (C1–C5)
- Cervicothoracic (C6–T2)
- Thoracolumbar (T3–L3)
- Lumbosacral (L4–S3).

#### Lower motor neurons

Lower motor neurons (LMNs) are efferent neurons connecting the central nervous system to an effector organ such as a gland or a muscle.

The cell bodies of LMNs are located within the grey matter of the cervicothoracic intumescence (spinal cord segments C6–T2) for the thoracic limbs and lumbosacral intumescence (segments L4–S3) for the pelvic limbs. Lesions at the level of these intumescences result in LMN signs in the corresponding limb(s).

# Clinical signs of dysfunction of the spinal cord

Figures 2.10 to 2.14 list the abnormalities found on neurological examination of patients with spinal cord disease.

The typical order in which functions are lost with progressive spinal cord disease are:

- 1. Conscious proprioception
- 2. Motor function
- 3. Bladder function
- 4. Deep pain perception.

Function	Abnormalities
Mental status	Unaltered
Cranial nerves	May be ipsilateral Horner's syndrome
Posture/gait	Paresis/paralysis of all four limbs (tetraparesis/ plegia) or of ipsilateral thoracic and pelvic limbs (hemiparesis/plegia) May be torticollis or scoliosis from asymmetrical paraspinal muscle weakness
Postural reactions	Postural reaction deficits in all four limbs or in ipsilateral thoracic and pelvic limbs
Spinal reflexes	Normal to increased spinal reflexes in all four limbs
Normal to increased tone in all four lim No muscle atrophy in any of the limbs	
Sensation	May be hyperaesthesia of the cervical spine
Other findings	Respiratory difficulty in tetraplegic patients Urinary retention

Clinical signs caused by lesions in the C1–C5 spinal cord segments.

Function	Abnormalities		
Mental status	Unaltered		
Cranial nerves	May be ipsilateral Horner's syndrome		
Posture/gait	Paresis/paralysis of all four limbs (tetraparesis plegia), of ipsilateral thoracic and pelvic limbs (hemiparesis/plegia) or of one thoracic limb (monoparesis)  There may be torticollis from asymmetrical paraspinal muscle weakness		
Postural reactions	Postural reaction deficits in all four limbs, in ipsilateral thoracic and pelvic limbs or in one thoracic limb		
Spinal reflexes	Normal to increased spinal reflexes in pelvic limbs Decreased to absent spinal reflexes in thorac limb(s)		
Muscle tone/mass	Normal to increased tone in pelvic limbs Decreased to absent tone in thoracic limb(s) Muscle atrophy in thoracic limb(s) No muscle atrophy in the pelvic limbs		
Sensation	Reduced/absent ipsilateral cutaneous trunci reflex if C8–T1 segment involved May be hyperaesthesia over caudal cervical/ cranial thoracic spine		
Other findings	Respiratory difficulty in tetraplegic patients Urinary retention		

Clinical signs caused by lesions in the C6–T2 spinal cord segments.

Function	Abnormalities		
Mental status	Unaltered		
Cranial nerves	Unaltered		
Posture/gait	Paresis/paralysis of pelvic limbs (paraparesis/ plegia) (Schiff–Sherrington phenomenon possible in acute and severe lesion)		
Postural reactions	Normal in thoracic limbs Postural reaction deficits in pelvic limbs		
Spinal reflexes	Normal in thoracic limbs  Normal to increased spinal reflexes in pelvilimbs		
Muscle tone/mass	Normal to increased tone in pelvic limbs No muscle atrophy in pelvic limbs		
Sensation	Reduced/absent cutaneous trunci reflex caudal to the level of the last intact dermatome Hypo/anaesthesia of the pelvic limbs May be hyperaesthesia of thoracolumbar spine		
Other findings	Urinary retention (UMN bladder)		

Clinical signs caused by lesions in the T3–L3 spinal cord segments.

Function	Abnormalities	
Mental status	Unaltered	
Cranial nerves	Unaltered	
Posture/gait	Paresis/paralysis of both pelvic limbs (paraparesis/plegia) or one pelvic limb (monoparesis)	
Postural reactions	Normal in the thoracic limbs Postural reaction deficits in both or one pelvic limb	
Spinal reflexes	Normal in the thoracic limbs Decreased to absent patellar reflex (uni- or bilateral) Intact pelvic limb withdrawal reflex	
Muscle tone/mass	Decreased to absent pelvic limb extensor muscle tone Muscle atrophy in the quadriceps femoris muscle	
Sensation	Hypo/anaesthesia restricted in dermatomal distribution over limbs May be hyperaesthesia over lumbar spine	
Other findings	Urinary retention (UMN bladder)	

Clinical signs caused by lesions in the L4–L6 spinal cord segments.

Function	Abnormalities		
Mental status	Unaltered		
Cranial nerves	Unaltered		
Posture/gait	Paresis of both pelvic limbs (paraparesis) or one pelvic limb (monoparesis) characterized to difficulty rising and plantigrade stance. Ability walk remains intact Paresis/paralysis of tail		
Postural reactions	Normal in the thoracic limbs Postural reaction deficits in both or one pelvic limb		
Spinal reflexes	Normal in the thoracic limbs Decreased to absent pelvic limb withdrawal reflexes (uni- or bilateral) Pseudo-hyperreflexic patellar reflex (uni- or bilateral) Decreased to absent perianal and/or perinea reflex		
Muscle tone and mass	Flaccid/decreased pelvic limb and tail muscle tone Dilated anal sphincter Muscle atrophy in the caudal thigh, hip and/or distal pelvic limb muscles		
Sensation	Hypoaesthesia in the pelvic limb, perineal area and tail May be hyperaesthesia in the (lumbosacral) LS spine/rectal palpation		
Other findings	Urinary incontinence (LMN bladder) Faecal incontinence		

Clinical signs caused by lesions in the L6–S3 spinal cord segments (cauda equina) (correlates to L3–S3 vertebrae).

# **Peripheral nerves**

# **Anatomy and function**

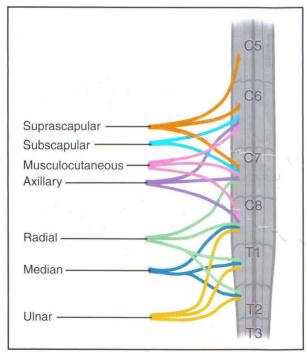
The peripheral nervous system consists of 12 pairs of cranial nerves and 36 pairs of spinal nerves that extend from or to the spinal cord and brainstem. Peripheral nerves contain both motor and sensory axons. The motor axons extend from neurons located in the ventral horn of the spinal cord or grey matter of the brainstem. The sensory axons have their cell body in the dorsal root ganglion or in homologous ganglia of cranial nerves. Most spinal nerves leave the vertebral canal through intervertebral foramina formed between the pedicles of adjacent vertebrae.

- A cutaneous region innervated by afferent nerve fibres from a single spinal nerve is called a dermatome.
- The musculature innervated by a single spinal nerve is termed a myotome.

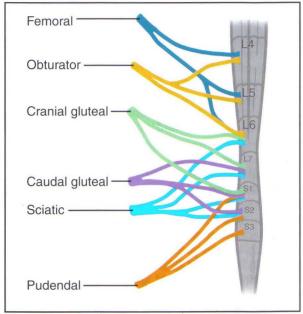
Individual muscles are innervated by multiple spinal nerves. In the limbs, muscles are supplied by nerves arising from either the brachial or lumbosacral plexi that consist of intermingled nerve fibres from the ventral branches of spinal nerves. The brachial plexus (formed by the ventral branches of the sixth, seventh and eight cervical and the first two thoracic spinal nerves) serves the thoracic limb (Figure 2.15) while the lumbosacral plexus (formed by the last five lumbar nerves and the three sacral nerves) serves the pelvic limb (Figure 2.16).

# Clinical signs of dysfunction of peripheral nerves

Figure 2.17 lists the abnormalities found on neurological examination of patients with peripheral nerve disease.



2.15 Cervicothoracic spinal cord segment, indicating nerve origins.



Lumbosacral spinal cord segment, indicating nerve origins.

Function	Abnormalities		
Mental status	Unaltered		
Cranial nerves	Variable involvement, dependent on disease. VII, IX and X commonly affected in generalized neuropathies (see Chapter 11)		
Posture/gait	Flaccid paresis/paralysis of affected limb(s) (motor)		
Postural reactions	Postural reaction deficits in affected limb(s) (sensory)		
Spinal reflexes	Decreased to absent spinal reflexes in affecte limb(s)		
Muscle tone	Decreased to absent tone in affected limb(s) (motor) Muscle atrophy in affected limb(s) (motor)		
Sensation	Decreased to absent nociception and sensation Paraesthesia		
Other findings	Self-mutilation		

Clinical signs caused by lesions of the peripheral nerves.

# **Neuromuscular junction**

# Anatomy and function

The neuromuscular junction consists of an axon terminal, a synaptic cleft, and the endplate region of a skeletal muscle fibre (see Chapter 17).

This junction is a transducer, converting electrical signals (nerve impulses) to chemical signals then back to electrical signals (muscle action potentials). The action potential in the nerve terminal depolarizes

the distal region of the axon, causing calcium channels on the axolemma to open. Calcium influx leads to a discharge of acetylcholine (ACh) vesicles via exocytosis into the synaptic cleft, and the released acetylcholine binds to the receptors located in the endplate region of the skeletal muscle fibres. This mechanism opens sodium and potassium channels and generates a local depolarization, triggering the action potential and subsequent muscle fibre contraction.

# Clinical signs of dysfunction of the neuromuscular junction

Transmission of the electrical impulse from the axon to the muscle fibre may be disturbed at a number of locations. Disorders of the neuromuscular junction are classified as presynaptic (e.g. botulism or tick paralysis; Chapter 14), postsynaptic (e.g. congenital or acquired myasthenia gravis; Chapter 17), or enzymatic disorders (e.g. organophosphate and carbamate toxicity).

- Presynaptic disorders result in a decrease in the quantity of ACh released. Clinically, the animals present with LMN-type deficits in all limbs (severe hypotonia and hyporeflexia). Cranial nerves may be involved, leading to dysphagia, dysphonia and facial weakness (see Chapters 11 and 13).
- Postsynaptic disorders are due to interference with the ACh receptor activation mechanism. Typically, affected animals present with exercise-induced weakness that improves following rest. The neurological examination is normal during periods of normality following rest.
- Enzymatic disorders: chemical compounds can interfere with acetylcholinesterase, the enzyme that inactivates ACh in the synapse. Clinical signs manifest as autonomic nervous system overstimulation and neuromuscular dysfunction, and are often similar to those of postsynaptic disorders (stiff, rigid gait with muscle tremors and exercise intolerance).

# Muscle

# Anatomy and function

Skeletal muscle functions to maintain body posture, produce movement and provide a reservoir source of energy. It is an integral part of the motor unit, which is composed of the LMN (cranial nerve nucleus or ventral horn cell body and axon extending along a peripheral nerve), the neuromuscular junction and the muscle fibres innervated. The motor unit is the final common pathway for motor activity and the muscle is the final effector of this motor unit. The functional cellular unit is the muscle fibre, or myofibre. Each muscle fibre is composed of several hundred myofibrils, which in turn contain several hundred myofilaments (actin and myosin proteins). The number of myofibres innervated by one

motor neuron varies according to the muscle group: muscles responsible for coarse movement (e.g. antigravity muscles) have large motor units, whereas those responsible for fine movements (e.g. extraocular muscles) have small motor units.

# Clinical signs of dysfunction in muscles

Figure 2.18 lists the abnormalities found on neurological examination of patients with muscle disease.

Function	Abnormalities		
Mental status	Unaltered		
Cranial nerves	Reflexes may be altered by involvement of facial muscles or muscles of mastication and swallowing		
Posture/gait	Stiff and stilted gait – tetraparesis Exercise-induced weakness/stiffness		
Postural reactions	Unaltered to altered if severe weakness		
Spinal reflexes	Unaltered (unless severe muscle atrophy/ fibrosis)		
Muscle tone/mass	Normal, increased or decreased tone Muscle atrophy or hypertrophy Limited joint movement due to muscle contractures		
Sensation	Usually unaltered, but can have hyperaesthesia of muscles		

2.18

Clinical signs caused by lesions in skeletal muscle.

# **Differential diagnosis**

The formation of a differential diagnosis list is essential in choosing and interpreting any diagnostic test, however sophisticated the test may be. The aim of performing such diagnostic tests should only be to confirm or exclude the differentials in the list, and not to replace the clinical evaluation. The differential diagnosis list can be developed taking into account the following:

- Signalment (see Appendix 1: Breed-specific disorders)
- Historical data: Questioning the owner should be aimed at defining the onset and progression of the condition. Furthermore, historical data can give clues as to how widespread or focal the disease process is in the nervous system, whether there is evidence of asymmetry, and how severe the signs have been
- Neurological findings: The aim of the neurological evaluation is to define the lesion localization (forebrain, brainstem, cerebellum, spinal cord segments, peripheral nerves, neuromuscular junction and muscles) and distribution of the disease (focal, multifocal, diffuse) within the nervous system.

# Disease processes

Disease processes that can affect the nervous system can be classified according to the cause, using the mnemonic DAMNITV:

- D Degenerative
- A Anomalous
- M Metabolic
- N Neoplastic, Nutritional
- I Inflammatory, Infectious, Idiopathic
- T Traumatic, Toxic
- V Vascular

Each of these disease processes has a typical signalment, onset and progression, as well as distribution within the nervous system (Figures 2.19 and 2.20).

## Acute, progressive with asymmetrical signs

Degenerative (e.g. intervertebral disc disease)

Neoplastic

Inflammatory/infectious disease

## Acute, progressive with symmetrical signs

Metabolic disorder

Nutritional disorder

Neoplastic

Inflammatory/infectious disease

Toxicity

### Acute, non-progressive (often asymmetrical)

Idiopathic

Trauma

Vascular disorders

## Chronic, progressive with symmetrical signs

Degenerative disorders

Anomalous disorders

Metabolic disorders

Neoplastic disorders Nutritional disorders

Inflammatory/infectious disease

Toxicity

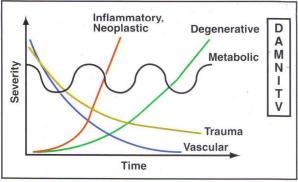
## Chronic, progressive with asymmetrical signs

Degenerative (e.g. intervertebral disc disease)

Neoplastic disease

Inflammatory/infectious disease

Disease categories based on onset and progression of signs. These are only guidelines, based on the most common disease course.



Onset and progression of neurological diseases of differing causes.

# Degenerative diseases

Degenerative diseases can affect any part of the nervous system. They typically have an insidious onset and slow progression.

Many degenerative diseases, which involve morphological degeneration of the nervous tissue, are familial or hereditary.

The age of onset is variable: some may affect young animals shortly after birth (e.g. most cerebellar abiotrophies); less frequently, adult animals may be affected (e.g. degenerative myelopathy, degenerative disc disease). These diseases often affect the nervous system in a symmetrical fashion.

## **Anomalous diseases**

Neurological signs can result from malformations that directly involve the nervous tissue (e.g. hydrocephalus, chiari-like malformations) or that involve the tissue surrounding the neuraxis (cranium and vertebral column). In patients with nervous tissue malformations, clinical signs are usually non-progressive or slowly progressive early in life.

Cranium or vertebral malformations do not always affect the nervous system and are often incidental findings on imaging.

If present, neurological disease caused by cranium or vertebral malformations is usually recognized early in life and signs tend to be non-progressive or slowly progressive. Occasionally, vertebral malformations do not result in neurological signs until adulthood, as a result of stenosis of the vertebral canal, progressive deformity or instability. Such malformations can also cause an acute onset of signs if, for example, stability is suddenly lost, as in the case of atlantoaxial subluxation.

## Metabolic disorders

Metabolic disorders can affect animals of any age. Clinical onset of neurological signs is variable but is most often acute, even though accompanying signs of systemic disease are often subacute to chronic. Diffuse non-specific signs, bilaterally symmetrical deficits referable to the forebrain, or symmetrical peripheral neuropathies are the most common signs. Most of these conditions tend to wax and wane with time.

## Neoplastic disorders

Neoplasia is more common in animals over 5 years but can occur at any age. Neurological signs are usually chronic and progressive in nature, although acute deterioration can be seen (especially if associated with spontaneous haemorrhage, impairment of vascular supply or loss of a compensatory mechanism to the normal surrounding tissue). Other factors determining the clinical expression of neoplasia are lesion size, histological nature, growth rate, associated inflammatory response, and location within the central *versus* peripheral nervous system. Neurological deficits can be asymmetrical or symmetrical, and often suggest a focal lesion. Paraneoplastic neurological syndromes can be seen.

#### **Nutritional diseases**

Nutritional diseases affecting the nervous tissue are rare in dogs and cats nowadays, as a result of the excellent balanced diets available. As with metabolic disease, neurological signs are typically bilaterally symmetrical. Their onset is variable (acute or insidious onset) and they are often slowly progressive. Their distribution can be diffuse or multifocal, as some nutritional diseases can affect selective areas of the CNS.

## Inflammatory and infectious diseases

Sterile inflammatory or infectious diseases can have an acute, subacute or a more insidious onset, depending on the cause. Signs usually progress without treatment, although the signs may wax and wane in some cases early after the onset. Neurological deficits can refer to a focal or multifocal lesion and can be asymmetrical or symmetrical.

## Idiopathic disorders

Idiopathic disorders tend to produce an acute onset of non-progressive or regressive signs. Neurological deficits vary with each syndrome. The term should be reserved for specific documented conditions or syndromes of unknown aetiology rather than for cases where a diagnosis could not, or has not, been confirmed.

#### **Trauma**

Traumatic disorders often have a peracute or acute onset. Signs usually remain static or improve over time. Neurological deficits can be symmetrical or asymmetrical, and often refer to a focal lesion; however, multiple lesions can frequently exist. Worsening of oedema (associated with secondary injury phenomena; see Chapter 19) can result in progression of neurological signs for a short period of 24-72 hours. and undetected spinal instability can cause a late deterioration in signs.

### **Toxic disorders**

Numerous toxins can affect the nervous system, either primarily or secondarily. Toxicities often produce acute onset disease and diffuse or bilaterally symmetrical signs from the time of the onset.

### Vascular disorders

Vascular disorders can result from loss of blood supply (ischaemia/infarction) or from haemorrhage into the nervous system. They are characterized clinically by a peracute or acute onset of non-progressive or regressive signs. Deficits are usually initially focal and often asymmetrical. Worsening of oedema (associated with secondary injury phenomena) can result in progression of neurological signs for a short period of 24-72 hours. Haemorrhage may be an exception, and can be responsible for a more progressive onset over a very short period of time. Clinical signs usually regress after 24-72 hours; this is attributable to diminution of the mass effect secondary to haemorrhage and reorganization or oedema resolution.

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# **Clinical pathology**

# Heather Wamsley and A. Rick Alleman

## Introduction

Laboratory evaluation of patients presenting with neurological diseases can be challenging, due to the numerous assays that might be performed on these patients and the non-specific results that are often obtained from routinely performed laboratory tests. However, when coupled with signalment, clinical findings and other ancillary diagnostics (e.g. imaging techniques), laboratory tests can be extremely valuable in the accurate identification of a number of conditions that affect neurological and neuromuscular function. This chapter reviews current information regarding laboratory assays useful in the assessment of patients with neurological and neuromuscular disease. Alterations in commonly performed laboratory tests are featured, as well as specific assays that can be used to identify definitively patients with selected disorders, when signalment, clinical findings or ancillary diagnostics prompt further laboratory investigation.

# Standard minimum database

Performing the standard minimum database (MDB) of tests is always indicated in cases of neurological and neuromuscular disease:

- Complete blood cell count (CBC) and examination of peripheral blood films
- Serum biochemistry
- Urinalysis.

Although patients that have disease restricted to the central nervous system (CNS) often do not exhibit specific MDB findings, these tests can be useful in detecting systemic diseases that may have neurological manifestations. Additionally, specific findings in the MDB may direct further diagnostic testing. This section details significant MDB abnormalities that may be detected in cases of neurological disease. Figure 3.1 provides a detailed list of diseases that may manifest concurrent neurological signs and MDB abnormalities.

Disorder	Haematology abnormalities	Biochemistry abnormalities	Urinalysis abnormalities
Degenerative			
Lysosomal storage disease	Inclusions within WBCs		
Muscular dystrophy		† CK;† AST	Myoglobinuria
Metabolic			
Hepatic failure/ hepatoencephalopathy (e.g. portovascular anomaly, cirrhosis)	Microcytosis (reduced mean cell volume of erythrocytes), usually without anaemia	↑ ALT and other hepatocellular enzymes; ↑ ALP and other cholestatic markers; hypoalbuminaemia; ↓ BUN; hypoglycaemia; hypocholesterolaemia	Ammonium urate crystalluria
Renal failure/uraemic encephalopathy	Normocytic, normochromic, non-regenerative anaemia	Azotaemia; hyperkalaemia; hyperphosphataemia; hypo/hypercalcaemia; hypernatraemia; increased anion-gap metabolic acidosis .	Inappropriately low urine specific gravity
Diabetes mellitus	Mild normocytic, normochromic, non-regenerative anaemia	Hyperglycaemia; hypercholesterolaemia; hypertriglyceridaemia; hepatocellular enzymes (e.g. ALT); hepatocellular enzymes (e.g. ALT); cholestatic markers (e.g. ALP)	Glucosuria; ketonuria; bacteruria ± pyuria
Hypothyroidism	Mild normocytic, normochromic, non-regenerative anaemia	Hypercholesterolaemia	
Hyperthyroidism	† Heinz bodies	† hepatocellular enzymes (e.g. ALT); † ALP	

Minimum database abnormalities in diseases that may manifest concurrent neurological signs. ALP = alkaline phosphate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen. (continues)

# Chapter 3 Clinical pathology

Disorder	Haematology abnormalities	Biochemistry abnormalities	Urinalysis abnormalities
Metabolic (continued)			
Hypoadrenocorticism	Variable anaemia (typically mild normocytic, normochromic, non-regenerative anaemia; severe anaemia with chronic disease or severe gastrointestinal haemorrhage); N to↑ eosinophil count; N to↑ lymphocyte count	Hyponatraemia; hyperkalaemia; hypochloraemia; hypercalcaemia; Na:K ratio <27; hypoglycaemia; azotaemia; metabolic acidosis	Inappropriately low urine specific gravity
Hyperadrenocorticism/ hypercortisolaemia	Stress leucogram shows mature neutrophilia, monocytosis, lymphopenia, eosinopenia	↑ ALT; ↑ ALP; hypercholesterolaemia; lipaemia; hyperglycaemia; N or ↓ BUN; hypernatraemia; hypokalaemia; hypophosphataemia	Isosthenuria; bacteruria ± pyuria
Hyperchylomicronaemia- associated neuropathy in cats	Lactescent fasting blood sample	Persistent fasting hypertriglyceridaemia	The Land County
Hypoglycaemia		Neurological signs usually apparent when ≤2.5 mmol/l (<45 mg/dl)	
Hyperglycaemia		Neurological signs usually apparent when ≥55.5 mmol/l (>1000 mg/dl)	
Hypocalcaemia		Neurological signs usually apparent when total calcium ≤1.9 mmol/l (<7.5 mg/dl), depending on ionized calcium levels	
Hypercalcaemia		Neurological signs usually apparent when total calcium ≥3.5–4.0 mmol/l (>14–16 mg/dl), depending on ionized calcium levels	
Hypokalaemia		Neurological signs usually apparent in cats when <3.0–3.5 mmol/l (<3.0–3.5 mEq/l) and in dogs when <2.5 mmol/l (<2.5mEq/l)	
Hyperkalaemia		Neurological signs usually apparent when >6.5mmol/l (>6.5 mEq/l)	
Hypomagnesaemia		Neurological signs usually apparent when when <0.4 mmol/l (<1.0 mg/dl)	
Severe hypermagnesaemia		Neurological signs usually apparent when >4.1 mmol/l (>10.0 mg/dl)	
Hyponatraemia		Neurological signs usually apparent when <125 mmol/l (<125 mEq/l)	
Hypernatraemia	e e	Neurological signs usually apparent when >170 mmol/l (>170 mEq/l)	
Hypophosphataemia		Neurological signs usually apparent when in cats <0.6–0.8 mmol/l (<2.0–2.5 mg/dl) and in dogs <0.5 mmol/l (<1.5 mg/dl)	
Hypo-osmolality		Neurological signs usually apparent when <250 mmol/kg, depending on rate of change	
Hyperosmolality		Neurological signs usually apparent when >350-360 mmol/kg, depending on rate of change	
Нурохіа	Anaemia; methaemoglobinaemia; carboxyhaemoglobinaemia	1 3 4 3 m 1	TOTAL STATE
Neoplastic			
CNS lymphoma or multicentric lymphoma with paraneoplastic polyneuropathy	Atypical lymphocytosis or lymphocytic leukaemia		कर्तासम्बद्धाः
Hyperviscosity syndrome	Increased rouleaux formation; absolute polycythaemia (primary, polycythaemia vera; secondary, e.g. renal neoplasia)	Hyperproteinaemia due to monoclonal gammopathy	
Insulinoma		Hypoglycaemia	100

(continued) Minimum database abnormalities in diseases that may manifest concurrent neurological signs. ALP = alkaline phosphate; ALT = alanine aminotransferase; BUN = blood urea nitrogen; N = normal. (continues)

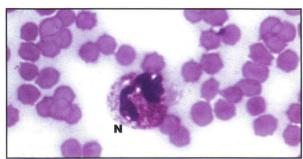
Disorder	Haematology abnormalities	Biochemistry abnormalities	Urinalysis abnormalities
Immune	the late court of the	ist and Workship Southern	Shiprakilya ba'a ka'a kilina katak
mmune myositis of masticatory muscles	Mild normocytic, normochromic, non-regenerative anaemia; neutrophilia; eosinophilia	CK;    AST; hyperglobulinaemia	Proteinuria
Myasthenia gravis with pneumonia	Inflammatory leucogram with toxic change		
SLE-associated polyneuropathy	Inflammatory leucogram	Azotaemia; hypoalbuminaemia; hypercholesterolaemia	Proteinuria
Infectious			
Acute canine distemper viraemia	Round eosinophilic RBC and/or WBC inclusions; lymphopenia		
Discospondylitis	Inflammatory leucogram	Hyperglobulinaemia, usually polyclonal gammopathy	Bacteruria; pyuria
Feline infectious peritonitis	Inflammatory leucogram	Hyperglobulinaemia, usually polyclonal gammopathy	
Feline immunodeficiency virus	Normocytic, normochromic, non-regenerative anaemia; neutropenia; thrombocytopenia	† hepatocellular enzymes (e.g. ALT); azotaemia; gammopathy, usually polyclonal	Proteinuria
Feline leukaemia virus	Macrocytic (often) or normocytic, normochromic, non-regenerative anaemia; neutropenia; lymphopenia; thrombocytopenia	hepatocellular enzymes (e.g. ALT); hyperbilirubinaemia; azotaemia; gammopathy, usually polyclonal	Proteinuria
Infectious meningoencephalitis (e.g. bacterial, fungal)	Inflammatory leucogram		
Tick-borne infections	Thrombocytopenia; mild normocytic, normochromic, non-regenerative anaemia; inflammatory leucogram; leucocytes containing morulae (Ehrlichia spp., Anaplasma phagocytophilum); spirochaetaemia (Lyme disease – Borrelia burgdorferi)		
Inflammatory	cestorie (1800) - National		CONTROL SUPPLE
Myositis/myopathy	Eosinophilia, if secondary to protozoal infection	† CK;† AST	Myoglobinuria
Steroid-responsive meningitis	Often neutrophilia, rarely neutropenic		
Toxic			
Ethylene glycol toxicity		Azotaemia; hypocalcaemia; hyperkalaemia; hyperphosphataemia; hypernatraemia; marked hyperglycaemia (in cats >350 mg/dl i.e. >19.4 mmol/l); severely increased aniongap metabolic acidosis; hyperosmolality with increased osmolal gap	Inappropriately low urine specific gravity; calcium oxalate monohydrate crystalluria (early)
Lead toxicity	Aberrant metarubricytosis (nucleated RBCs); basophilic stippling; normal hematocrit or mild normocytic, normochromic, non-regenerative anaemia		
Metaldehyde toxicity		Increased anion-gap metabolic acidosis	Light the Contract to the Cont
Strychnine toxicity		CK levels;    AST; metabolic acidosis due to lactic acidaemia	Myoglobinuria

(continued) Minimum database abnormalities in diseases that may manifest concurrent neurological signs.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; RBC = red blood cell; SLE = systemic lupus erythematosus; WBC = white blood cell.

# Chapter 3 Clinical pathology

Specific MDB findings are not observed in most cases of degenerative and anomalous neurological diseases with one exception: leucocyte inclusions are identified uncommonly in the peripheral blood and cerebrospinal fluid (CSF) of patients with lysosomal storage disease (Figures 3.2 and 3.3).



Peripheral blood film from a Siamese cat with mucopolysaccharidosis VI. The neutrophil (N) contains granular eosinophilic cytoplasmic inclusions, which are the result of accumulation of substrate material that is normally degraded by the deficient lysosomal enzyme. Wright–Giemsa stain; original magnification X250. (Courtesy of John W Harvey)

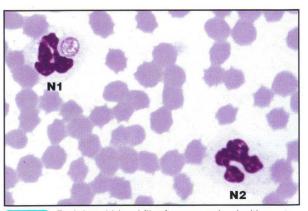


Spinal fluid from a Muntjac deer with  $\mathrm{GM}_2$ -gangliosidosis. Several macrophages containing linear eosinophilic cytoplasmic inclusions are seen. The inclusions are the result of accumulation of substrate material that is normally degraded by the deficient lysosomal enzyme. Wright–Giemsa stain; original magnification X250.

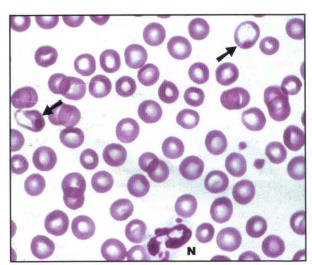
Many metabolic diseases (see Figure 3.1) manifest concurrent neurological and MDB abnormalities. Neurological signs can be the result of a single electrolyte abnormality (such as hypocalcaemia) that has multiple differential diagnoses. These differentials are not presented here; the reader is referred to an internal medicine or clinical pathology text for in-depth discussion of this topic. Identification of specific serum biochemical abnormalities may prompt additional clinical pathology testing (e.g. bile acids; see below).

A few neoplasms uncommonly demonstrate concurrent neurological and haematological abnormalities, such as: CNS lymphoma associated with leukaemia; polycythaemia vera or renal neoplasia associated with absolute polycythaemia; and multiple myeloma associated with hyperviscosity due to monoclonal gammopathy. In older adult large-breed dogs that are hypoglycaemic, insulinoma should be considered as a differential diagnosis.

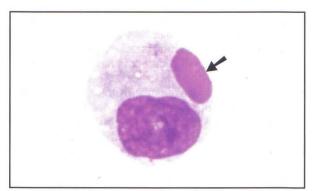
Specific MDB findings are not observed in most cases of infectious, inflammatory, immune-mediated and ischaemic neurological diseases with some rare exceptions. Ehrlichia or Anaplasma morulae (Figure 3.4) or Borrelia spirochaetes are identified infrequently during examination of peripheral blood films from infected animals. These animals are often thrombocytopenic; however, this finding is non-specific. Erythrocyte and leucocyte inclusions are identified uncommonly in the peripheral blood and CSF of dogs that have acute canine distemper viraemia (Figures 3.5 and 3.6). The intensity and colour of the inclusions depends upon the type of stain used to prepare the peripheral blood film. The inclusions are more easily identified when aqueous Wright's stain is used. The inclusions are variably sized, round and intensely eosinophilic. When stained with Wright-Giemsa, the inclusions are pale blue-green (Harvey, 2001).



Peripheral blood film from an animal with acute granulocytic ehrlichiosis. The neutrophil N1 contains a morula of several small rod-shaped bacteria – Anaplasma phagocytophilum (formerly Ehrlichia equi, Ehrlichia phagocytophilia and Human Granulocytic Ehrlichiosis agent). Although this blood film is from a horse, the organism can also infect dogs, humans and some ruminants. Wright–Giemsa stain; original magnification X250.



Peripheral blood film from a dog with acute canine distemper virus infection. Two erythrocytes (arrowed) contain large distemper virus inclusions. A neutrophil (N) contains three variably sized and shaped cytoplasmic inclusions. Diff-Quik stain; original magnification X250. (Courtesy of John W Harvey)



Spinal fluid from a dog with acute canine distemper virus infection. The large mononuclear cell contains a distemper virus inclusion (arrowed). Wright–Giemsa stain; original magnification X250.

The severity and specificity of MDB changes that occur with different intoxications are variable. The most dramatic example is ethylene glycol toxicity, which can cause marked changes in the serum biochemical profile. MDB changes suggestive of secondary acute renal failure are seen (e.g. azotaemia, hyperkalaemia, hyperphosphataemia). These observations, coupled with the more specific findings of moderate to marked hypocalcaemia, increased osmolal gap (detailed below) and calcium oxalate monohydrate crystalluria (which occurs early during the intoxication), are strongly suggestive of ethylene glycol intoxication. With lead toxicity, basophilic stippling (25% of cases), marked metarubricytosis (50%), and increased nucleated red blood cells, in the absence of an associated polychromasia, may be seen (Fenner, 2000).

## Other biochemical assays

Specific analytes can be measured in the serum of neurological patients, either if indicated by abnormalities identified by the MDB tests or for therapeutic monitoring (e.g. thyroid hormone level). This section provides a brief overview of the tests that may be indicated during evaluation of a patient that has signs of neurological disease or during medical management of a previously diagnosed disease. Commercial laboratories can perform many of these tests; however, test availability and sample handling needs may vary with each laboratory. Local commercial laboratories should be checked for their specific sample-handling requirements.

# Anticonvulsant serum concentration

Since seizure control correlates with serum drug concentration and not the dosage, serum anticonvulsant monitoring is indicated for patients receiving such therapy. Serum concentration of phenobarbital should be measured 3–4 weeks after initiation of therapy or a dosage alteration (Levitski and Trepanier, 2000). If an initial loading dose is employed, the serum concentration should be measured 1 week later and then again in 3–4 weeks. During therapy for a controlled epileptic patient, the serum phenobarbital concentration should

be reassessed every 6–12 months. A recent report (Levitski and Trepanier, 2000) indicated that peak and trough phenobarbital concentrations do not vary significantly in most epileptic dogs and that samples intended for phenobarbital measurement can be collected randomly during the daily dosing interval, rather than during the anticipated trough period. However, in refractory cases, it may be advisable to measure peak and trough levels.

Serum concentration of potassium bromide should be measured 3–4 months after initiation of therapy or a dosage alteration in dogs, and after 2 months in cats. If an initial loading dose is employed, the serum concentration should be measured 1 week later and then again in 4 weeks. In a controlled epileptic patient, the serum bromide concentration should be reassessed every 6–12 months. Patients receiving potassium bromide will have spuriously elevated serum chloride concentrations due to the interaction of bromide with the reagents used in the test.

Less commonly used anticonvulsants, such as gabapentin, levetiracetam, zonisamide and felbamate, can also be assayed in the serum. Not all of the newer anticonvulsants have established canine therapeutic ranges and the optimal timing of sample collection in each case has not been determined. If necessary, advice can be gained from a neurologist or local diagnostic laboratory. Chapter 7 gives further information on anticonvulsants.

## Bile acids and ammonia

Pre- and postprandial bile acid measurements are indicated in cases of suspected hepatic dysfunction and for any patient that is to be given a hepatotoxic antiepileptic drug, such as phenobarbital. In cirrhosis, the serum bile acid concentration is typically moderately to markedly elevated in both the pre- and postprandial samples. In patients with portovascular anomaly, the preprandial serum bile acid concentration is typically normal or mildly elevated and the postprandial sample is typically moderately to markedly elevated. Recent reports suggest that measurement of randomly sampled urine sulphated and non-sulphated bile acids, effectively identifies cats and dogs that have clinically significant hepatic disease, with greater specificity than quantitation of serum bile acids and circumvents the need for pretest fasting (Balkman et al., 2003; Trainor et al., 2003).

To assess hepatic function, the resting ammonia concentration can be measured. This test is less sensitive than measurement of bile acids but is useful in patients with hepatic encephalopathy, as ammonia can be decreased fairly easily with medical management. Provocative ammonia tolerance testing is contraindicated for patients exhibiting hepatoencephalopathic signs but this test may be useful in the diagnosis of suspected portovascular anomalies in Maltese dogs that are not hepatoencephalopathic, since healthy Maltese dogs may have elevated postprandial bile acids, in the absence of a portovascular anomaly (Tisdall et al., 1995). Samples intended for ammonia measurement must be collected into an ice-chilled tube and assayed within 20 minutes of collection.

## Cholinesterase

In cases of suspected organophosphate or carbamate intoxication, exposure is confirmed by identification of blood cholinesterase activity decreased to < 25% of the control activity level (cholinesterase activity is greatest in erythrocytes of most domestic animals). Blood cholinesterase activity does not necessarily correlate with the severity of the clinical signs. Organophosphate inhibition of cholinesterase activity is stable. However, since carbamates reversibly bind cholinesterase, reactivation of carbamate-inhibited cholinesterase activity can occur during transport or laboratory determination of activity. Therefore, cholinesterase activity may spontaneously return to normal in cases of carbamate intoxication. Results should be interpreted in the light of the history of potential toxicant exposure, the clinical signs and appropriate response to therapy. Additionally, cholinesterase activity in tissues such as the brain (particularly the caudate nucleus), retina, liver, kidney, fat or hair can be measured on post-mortem examination. Organophosphates can also induce a delayedonset, dying-back peripheral neuropathy with demyelination 1-6 weeks after exposure. Suspicion of this condition may be raised by toxicant exposure history and results of nerve biopsy. As with acute intoxication, identification of decreased blood cholinesterase activity is confirmatory. Anecdotal clinical experience indicates that CSF cholinesterase is elevated above 300 IU/I during inflammatory CNS disease.

# Congenital disease testing

Dogs with von Willebrand disease (vWD) may uncommonly present with neurological signs due to CNS haemorrhage secondary to thrombopathia, which may be screened for by determination of the buccal mucosal bleeding time (see Tests of haemostasis). The diagnosis of vWD is substantiated by enzyme-linked immunosorbent assay (ELISA) quantitation of the amount of circulating von Willebrand factor (vWF) in the plasma. Plasma samples should be harvested from unclotted, non-haemolysed blood collected into ethylenediamine tetraacetic acid (EDTA) or citrate anticoagulant (clotting and haemolysis decrease the concentration of vWF). Samples should be analysed by a commercial laboratory that uses assays that have been validated for dogs and cats, since canine and feline vWF is antigenically different from human vWF.

Degenerative diseases, such as lysosomal storage diseases, or rare inborn errors of metabolism (e.g. L-2-hydroxyglutaric aciduria), may manifest as progressive tremors, ataxia, paresis, dementia and seizures. Lysosomal storage diseases, which typically cause signs in animals less than 2 years old, may be confirmed by specific enzyme assays (e.g. globoid cell leucodystrophy, i.e. Krabbe's disease) or genetic testing (e.g. fucosidosis). Abramson et al. (2003) identified six polioencephalopathic Staffordshire Bull Terriers aged from 4.5 months to 7 years as having an increased concentration of the organic acid L-2-hydroxyglutaric acid in their blood, urine and CSF, and disease manifestation similar to L-2-hydroxyglutaric aciduria in humans, which included seizures, ataxia, dementia and tremors. Additionally, these animals had increased

concentrations of the amino acid lysine in their urine and CSF. The exact metabolic error resulting in L-2-hydroxyglutaric aciduria is unknown but there may be an association with a defect in lysine metabolism. Urine organic acid and amino acid screening is a useful tool to document this disease and others like it, such as D-2-hydroxyglutaric aciduria, which has been reported once in a dog (Nyhan *et al.*, 1995). A neurologist or local diagnostic laboratory should be consulted for availability of tests to diagnose these rare diseases.

# **Endocrine testing**

A brief summary of endocrine testing is presented here. For greater detail see *BSAVA Manual of Canine and Feline Endocrinology*.

Total serum calcium abnormalities that are suspected of being clinically significant should be confirmed by measurement of the ionized calcium concentration, which may be performed using an inhouse analyser or sent to a commercial laboratory. Based upon the ionized calcium concentration and other clinical findings, assay of parathyroid hormone, parathyroid hormone-related protein and vitamin D concentrations may also be indicated.

Hypothyroidism may be associated with disorders of muscle, the peripheral nervous system (PNS) and the CNS. In dogs with appropriate clinical signs or moderate to marked hypercholesterolaemia, evaluation of thyroid function is indicated, such as the measurement of total thyroxine (T4), free T4 by equilibrium dialysis or thyroid-stimulating hormone. Feline hyperthyroidism may be associated with CNS or neuromuscular signs. In cats with appropriate clinical signs and/or hepatocellular enzyme elevation, evaluation of thyroid function is indicated (e.g. total T4).

Hypoadrenocorticism is a differential diagnosis for dogs with an episodic history of muscular cramping, neuromuscular weakness, collapse and consistent clinicopathological findings (e.g. hypoglycaemia, hyponatraemia, hyperkalaemia), which can be investigated by an adrenocorticotropic hormone (ACTH) stimulation test (Saito et al., 2002). Additionally, animals with hyperadrenocorticism may also present with neuromuscular or CNS signs due to a myopathy or the space-occupying effects of an expanding pituitary macroadenoma, respectively. Diagnostic evaluation of hyperadrenocorticism may involve an ACTH stimulation test, dexamethasone suppression test, measurement of endogenous ACTH, urine cortisol:creatinine ratio determination and abdominal ultrasonography.

The diagnosis of an insulinoma is supported by identifying an inappropriately high serum insulin concentration (often >20  $\mu\text{IU/ml})$  in a middle-aged to older animal that exhibits persistent fasting hypoglycaemia with glucose <3.3 mol/l (<60 mg/dl) or even <1.9 mmol/l (<35 mg/dl), and a history of episodic weakness or seizures associated with fasting, excitement, exercise or the postprandial period (2–6 hours after feeding). The blood sample for measurement of insulin should be taken while the animal's glucose concentration is below normal. This method of diagnosing beta-cell neoplasia is preferred over the use of the amended insulin:glucose ratio (formula below),

which is non-specific and can be abnormal (>30) with other causes of hypoglycaemia, in addition to insulinoma. The formula for the amended insulin:glucose ratio is:

(serum insulin (μIU/mI) x 100) ÷ (blood glucose (mg/dl) - 30)

As beta-cell tumours are typically very small, failure to detect a pancreatic mass using abdominal ultrasonography (which occurs in approximately 75% of dogs with an insulinoma) does not exclude insulinoma. The diagnosis is often made on the basis of appropriate signalment, history, clinical signs and laboratory findings (Feldman and Nelson, 1996). Measurement of serum fructosamine is occasionally indicated in the diagnosis and management of patients with diabetes mellitus. Fructosamine is a glycosylated protein whose serum concentration is directly proportional to the serum glucose concentration over the preceding 2-3 weeks. It is useful in cats to distinguish diabetic hyperglycaemia from transient stress-induced hyperglycaemia (Plier et al., 1998) and can be used as an indicator of glycaemic control during the medical management of diabetic patients, which may develop a diabetic neuropathy.

### Tests of haemostasis

Animals with haemorrhagic diatheses may present with neurological signs due to CNS haemorrhage. Coagulation cascade function can be assessed by determining the prothrombin time (extrinsic and common pathways). the activated partial thromboplastin time (intrinsic and common pathways) or the activated clotting time (intrinsic and common pathways). The platelet count per microlitre can be rapidly estimated during examination of a stained peripheral blood film by determining the average number of platelets per 100x high-power field, which is then multiplied by 15,000. The platelet count can also be determined using a haemocytometer or automated CBC machine. Counts obtained by these methods should always be verified by examination of the peripheral blood film. Once coagulopathy and thrombocytopenia have been excluded as the cause of a haemorrhagic diathesis, platelet function may be assessed by determination of the buccal mucosal bleeding time (see Chapter 14 for further details). Identification of a coagulopathy, thrombocytopenia or thrombopathia should prompt further diagnostic testing (e.g. specific coagulation factor assay, tick-borne disease titres, bone marrow cytology, vWF assay) to determine the underlying aetiology of the haemostatic defect.

# Blood lead concentration

In cases of suspected lead toxicity, identification of a blood lead concentration >40  $\mu$ g/ml is confirmatory. Half of these patients may exhibit aberrant metarubricytosis (nucleated RBCs) and one quarter may have basophilic stippling (Fenner, 2000).

## Markers of muscular injury

Evaluation of serum creatine kinase (CK) may be useful in suspected cases of myopathy or myositis. Since CK has a short half-life and is highly sensitive

and specific for skeletal and cardiac muscle injury, single measurements >10,000 IU/I or persistent elevations >2000 IU/I are considered clinically significant. However, with degenerative myopathies, CK levels may be normal or only mildly increased (Parent, 1999). The serum concentration of aspartate aminotransferase (AST) is also elevated with muscular injury and alanine aminotransferase (ALT) may be elevated with severe skeletal muscle necrosis. However, since these enzymes are also present in hepatocytes (ALT and AST), cardiac myocytes (AST) and erythrocytes (AST), they lack the tissue specificity of CK.

Plasma or blood lactate measurement is indicated for patients with suspected metabolic myopathy (e.g. pyruvate dehydrogenase deficiency in Sussex Spaniels). The lactate concentration is measured both before and after exercise. Typically the animal is exercised until signs are induced prior to taking the post-exercise sample. A lactate concentration that is dramatically increased above reference range in the sample collected after exercise is suggestive of a metabolic myopathy (Shelton, 1993; see Chapter 17). In addition to myopathy, lactate may be increased with an increased anion-gap metabolic acidosis due to lactic acidosis, as occurs with hypoperfusion (e.g. hypovolaemia) or decreased oxygen delivery to tissues (e.g. severe anaemia).

With significant muscle injury, myoglobinuria may occur and can be detected as a positive urine dipstick haem reaction. Once haematuria has been excluded by examination of the urine sediment, pigmenturia due to myoglobinuria may be distinguished from that due to haemoglobinuria by an ammonium sulphate precipitation test, which is available through most commercial laboratories or may be performed in-house. Mixing ammonium sulphate with urine followed by centrifugation causes haemoglobin to precipitate and myoglobin to remain in solution. This results in a red-brown precipitate (haemoglobin), red-brown supernatant (myoglobin) or red-brown precipitate and supernatant (haemoglobin and myoglobin).

# Serum osmolality and osmolal gap

Measurement of serum osmolality may be indicated in cases of suspected ethylene glycol intoxication or other hyperosmolar states (e.g. diabetic hyperosmolar non-ketotic syndrome). In addition to abnormalities consistent with acute renal failure, ethylene glycol intoxication is associated with a markedly increased anion-gap (40–50 mmol/l) metabolic acidosis. The osmolal gap, which is determined by subtracting the calculated serum osmolality from the actual measured serum osmolality, is normally 10–15 mmol/kg. Values >25 mmol/kg are suggestive of intoxication with osmotically active agents, such as ethylene glycol, mannitol or ethanol. The formula for calculation of serum osmolality (expressed as mmol/kg) is:

(1.86 x ([Na+] mEq/l + [K+] mEq/l)) + ([Glucose] mg/dl ÷ 18) + ([BUN] mg/dl ÷ 2.8) + 9

where BUN is blood urea nitrogen.

# Serum protein electrophoresis

Serum protein electrophoresis (SPE) is indicated when an increased serum globulin concentration has been identified. This test will identify whether there is polyclonal immunoglobulin production, as is seen with infectious, autoimmune or inflammatory disease, or whether there is monoclonal immunoglobulin production, as is seen with lymphoid neoplasia and rarely with chronic infectious diseases (e.g. ehrlichiosis, leishmaniasis, feline infectious peritonitis).

# Urine protein:creatinine ratio

Measurement of the urine protein:creatinine ratio (UPC) is indicated when the urine sediment is inactive (i.e. no cells or bacteria), to evaluate proteinuria, which may be present in, for example, patients with systemic lupus erythematosus. The UPC should be <1; values >1 raise concern for glomerular disease (glomerulonephritis, glomerulosclerosis, canine amyloidosis), Bence Jones proteinuria or, less commonly, tubular proteinuria.

# Serology and microbiology

Serological and microbiological testing are frequently indicated during evaluation of patients with neurological and neuromuscular disease, especially when inflammatory or autoimmune disease is suspected. Commercial laboratories typically perform many of these tests. Local laboratories should be checked for availability and sample handling requirements.

In suspected cases of myasthenia gravis, measurement of serum acetylcholine receptor antibody titre is indicated. In addition to blood and urine culture, measurement of serum *Brucella canis* titre is indicated in cases of discospondylitis. For patients that exhibit an unexplained CSF neutrophilic pleocytosis, bacterial meningitis should be a consideration and CSF bacterial culture is indicated, especially if degenerative changes are present in the neutrophils. Additionally, blood and urine cultures may aid in diagnosis. When fungal infection is suspected, serum and CSF fungal titres (e.g. *Aspergillus*), careful examination of the urine sediment for fungal elements and fungal culture of the urine are indicated.

In cases of inflammatory CNS disease, peripheral neuropathy or polymyositis, it may be useful to measure infectious disease and antinuclear antibody (ANA) titres. Figure 3.7 provides a list of infectious organisms that may be tested for during assessment of these patients. Factors such as history and clinical signs, likelihood of exposure to infectious agents based upon geography, vaccination status and client finances often dictate which titres are most useful and affordable.

In order to establish exposure to an infectious agent that may be the cause of disease, antibody titres are routinely measured to show that an immune response against a given organism has occurred. While antibody titres are extremely useful as supportive evidence of infection, problems such as previous natural exposure to the agent, previous vaccination against the agent, or assay cross-reactivity with antibodies formed against other infectious agents (e.g. feline infectious peritonitis virus and other coronavirides) may result in misleading

### Tick-borne

Ehrlichia spp.
Anaplasma phagocytophilum
Rickettsia rickettsii (Rocky Mountain spotted fever)
Borrelia burgdorferi (Lyme disease)

#### Viral

Canine distemper virus (CDV) <sup>a</sup>
Rabies virus
Feline leukaemia virus
Feline immunodeficiency virus
Feline infectious peritonitis (FIP) virus <sup>b</sup>

## Protozoal

Toxoplasma gondii Neospora caninum Babesia spp. Encephalitozoon cuniculi (rare) Leishmania spp. (rare)

#### Fungal

Blastomyces dermatitidis Cryptococcus spp. Histoplasma capsulatum Coccidioides immitis Aspergillus spp.

### Parasitic helminth

Dirofilaria immitis Angiostrongylus vasorum

### Bacterial

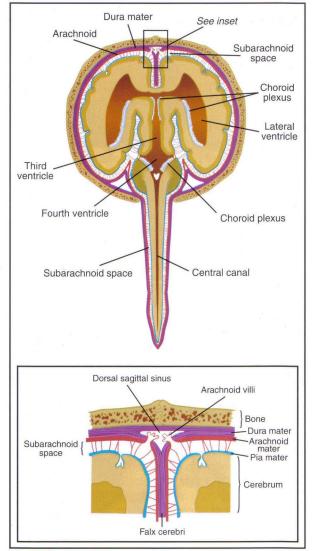
Brucella canis (discospondylitis)

3.7 Infectious organisms that may be detected serologically in patients with neurological and neuromuscular disease. <sup>a</sup> PCR may be more useful to diagnose CDV. <sup>b</sup> Serum and/or fluid protein electrophoresis or PCR may be more useful to diagnose FIP.

information regarding the diagnosis of an active infection as the cause of current neurological signs. In certain circumstances, polymerase chain reaction (PCR) analysis may be available and can be used for specific identification of active infection by a given agent. When optimized, this technique identifies active infection by detecting miniscule amounts of organism-specific DNA in tissues or body fluids. For example, in cases of ehrlichiosis, many *Ehrlichia* species can cause similar clinical diseases and interspecies cross-reactivity occurs with most antibody titre assays; therefore, PCR analysis can be used as a rapid method for definitive identification of the aetiological agent at the species level.

## Cerebrospinal fluid analysis

CSF is an ultra-filtrate of plasma that is produced predominantly by the choroid plexi within the ventricular system. CSF flows caudally through the ventricular system to the central canal of the spinal cord toward the cauda equina. It passes from the ventricular system through the CNS parenchyma to the subarachnoid space, where it is resorbed into the venous system via the arachnoid villi (Figure 3.8); a small



The ventricular system, depicting the neuroanatomical origins of CSF production and sites of absorption. Modified from De Lahunta (1983).

portion exits along the spinal nerve roots. CNS disease does not consistently cause alterations in CSF; abnormalities depend on the location and extent of the CNS lesion. Parenchymal, extradural and non-exfoliative lesions may cause minimal (e.g. protein elevation) or no change in the CSF. Additionally, the CSF leucocyte count does not correlate with CNS disease severity or prognosis; it simply reflects the degree of meningeal or ependymal cell involvement in the disease process.

CSF analysis is an ancillary diagnostic test that is indicated when a patient has neurological signs that are referable to the CNS. Ideally, CSF analysis should be performed prior to myelography to exclude meningitis, since clinical signs may be exacerbated by radio-opaque contrast agent-induced meningeal irritation. CSF collection requires general anaesthesia and is associated with uncommon but significant risks (Figure 3.9). These risks are minimized by employing proper anaesthetic and collection techniques and by excluding patients that have increased risk of complications

## Risks

General anaesthesia (e.g. hypotension, hypothermia, apnoea, bradycardia, arrhythmia)

Loss of airway patency during atlanto-occipital collection due to patient positioning and use of unguarded endotracheal tube (see Chapter 20) Cerebral and/or cerebellar herniation due to intracranial pressure change

CNS haemorrhage

Brainstem trauma due to needle puncture at atlanto-occipital site Spinal cord trauma due to needle puncture at lumbar site

### Contraindications

High risk of anaesthetic complications

Suspected increased intracranial pressure (e.g. progressive obtundation; papilloedema; miosis with responsive pupillary light reflex; intermittent extensor rigidity or opisthotonus)

Suspected active intracranial haemorrhage

Radiographic evidence of very large intracranial space-occupying masses

Severe hydrocephalus

Severe cerebral oedema on MRI

Haemorrhagic diathesis as a predisposition for iatrogenic CNS haemorrhage

Atlanto-occipital collection is contraindicated in cases of suspected atlantoaxial luxation or other causes of cervical vertebral instability

3.9

Risks and contraindications associated with CSF collection.

(e.g. those with increased intracranial pressure, ICP) (Figure 3.9). For information on the treatment that can be employed for patients with elevated ICP, see Chapters 8 and 19. To minimize the risks of CSF collection, the anaesthetic protocol can be manipulated in an attempt to decrease ICP. Drugs such as ketamine should be avoided in these patients. Patients with a suspected increased ICP may be given mannitol and ventilated to achieve and maintain a  $P_{\rm a}{\rm CO_2}$  of approximately 30–35 mmHg to reduce the ICP. Further details on the anaesthetic management of such patients can be found in Chapter 20.

During collection, CSF should *not* be aspirated by using negative pressure applied via a syringe attached directly to the needle hub. Aspiration can cause a rapid decrease in CSF pressure, which may trigger intracranial haemorrhage or herniation (cerebral and/or cerebellar). Similarly, removal of an excessive volume of CSF can potentiate haemorrhage or herniation, but 1 ml per 5 kg of bodyweight can be safely collected from most patients (Chrisman, 1992).

CSF is collected aseptically from the atlanto-occipital (AO) site; also referred to as the cerebellomedullary cistern (CMC) or cisterna magna; and/or from the caudal lumbar site, using materials listed in Figure 3.10. Collection from both sites is detailed below, though in small animals CSF is more commonly collected from the AO site. Collection from the AO site is less difficult, usually results in a larger sample volume, and is typically associated with less iatrogenic blood contamination. In cases of focal CNS disease, CSF samples are more likely to be abnormal or representative of the CNS when they are collected caudal to the lesion. Therefore, in

Hair clippers

Surgical scrub

Sterile gloves

Spinal needle (20- or 22-gauge, 11/2 inch for AO; 21/2 or 31/2 inch for lumbar)

Sterile collection container: 3 ml syringe, conical centrifuge tube, plain tube (free of anticoagulant), and/or an EDTA tube

3.10 Materials for CSF collection.

animals with lesions involving the spinal cord or canal, lumbar CSF samples are more consistently abnormal than AO samples. In this situation, it is preferable to collect CSF from both sites (Thomson *et al.*, 1990).

# **Atlanto-occipital CSF collection**

The procedure for AO CSF collection is illustrated in Figures 3.11 and 3.12.

With the patient in lateral recumbency with the dorsum near the table's edge, the nose is elevated to place the sagittal plane of the muzzle parallel to the table. The neck is then fully flexed and the ears are pulled rostrally. It is important to be aware that on full neck flexion there is a risk of the endotracheal tube kinking and interfering with anaesthesia. There are two ways to identify the AO space properly, using anatomical landmarks:

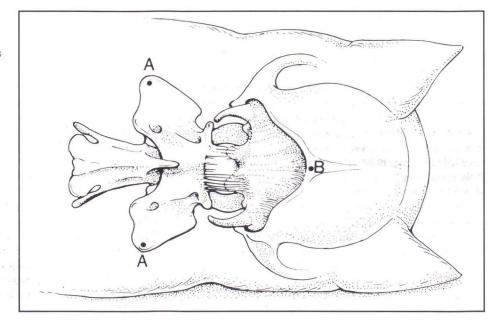
- Palpate a triangle of landmarks formed by the occipital protuberance and the most prominent points of the lateral wings of the atlas (Figure 3.11). The location for needle insertion is on the dorsal midline between the wings of the atlas, one-third to one-half of the way caudal to the occipital protuberance (the most cranial point of the triangle formed by the landmarks)
- Alternatively, use the occipital protuberance to identify the midline and use the most cranial margins of the wings of the atlas to identify the location of the AO space, which should be at the same level along the neck.





Atlanto-occipital CSF collection. (a) Proper positioning. (b) Close-up demonstrating CSF dripping from the hub of the spinal needle into the collection tube.

3.11 Anatomical landmarks for atlanto-occipital CSF collection. A = wing of atlas vertebra. B = occipital protruberance.



The needle is positioned directly on the midline, perpendicular to the neck, at the level of the AO space and advanced slowly 1-2 mm at a time. Once the skin has been penetrated, the stylet can be removed. One or two slight 'pops' may be felt as the needle is advanced through the muscle layers and meninges into the cisterna magna. Resistance will decrease when the dura is penetrated. When the subarachnoid space has been entered, CSF will appear in the needle hub. If blood is obtained, a few drops of CSF should be allowed to flow. If the fluid clears, it can be collected for analysis; if it remains bloody, the needle should be removed and the procedure started again. If the needle hits bone while being advanced, it may be redirected cranially or caudally, moving the needle off the bone into the AO space. If this is not possible, the needle may be removed and collection attempted again after reassessment of anatomical landmarks.

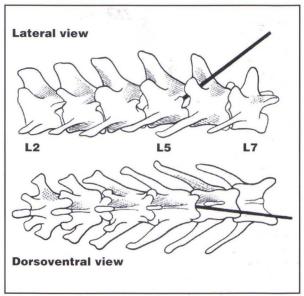
Once the needle is in place, fluid is collected either by allowing it to drip into a sterile collection tube or by suctioning the drops into a sterile syringe as they form at the spinal needle hub. Do not attach the syringe to the spinal needle hub and aspirate. The rate of CSF flow out of the needle may be enhanced by jugular compression but this should be avoided in cases with increased ICP. The minimum CSF volume required for a complete analysis is approximately 0.5 ml. Once a sufficient volume has been collected or the CSF flow stops, the spinal needle is removed from the cisterna. Several drops of CSF typically remain within the spinal needle; they can be forced out of the needle into the collection tube by replacing the stylet, while holding the end of the needle over the tube.

Ideally, CSF is collected into a sterile syringe or plastic tube, because cells may adhere to glass containers (Taylor, 1998; Fenner, 2000). If the sample is haemorrhagic, it should be placed in an EDTA tube to prevent clotting. Samples intended for bacterial culture should be free of anticoagulant. For optimal preservation of cytological details, CSF samples must be processed or preserved within 30 minutes of collection. This is discussed in more detail below.

## **Lumbar CSF collection**

Anatomical landmarks for lumbar CSF collection are shown in Figure 3.13.

With the patient in lateral recumbency, the lumbar spine is flexed. The appropriate intervertebral space is identified, which in dogs is L4-L5 or, preferably, L5-L6 and in cats L6-L7. This is done by palpating the ilial crests; the vertebral spinous process found immediately cranial to the ilial crests is that of L6. The needle is positioned on midline, just cranial to the appropriate vertebral spinous process, at a 45° angle with the needle point directed cranially. The needle is advanced as described above under AO collection but the stylet may be left within the spinal needle. When correctly positioned, the needle typically passes through or alongside the cauda equina/ caudal spinal cord, which often elicits a tail or leg twitch. The fluid is frequently collected from the ventral subarachnoid space. Beyond a tail or leg

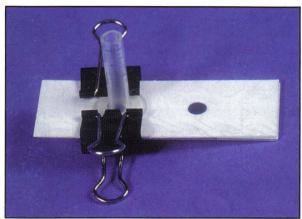


3.13 Anatomical landmarks for lumbar CSF collection. (Reproduced from Fossum *et al.* (1997) with permission from Elsevier.)

twitch or minor spinal cord haemorrhage with potential sample contamination, persistent untoward effects are not typically manifested as a result of this collection method (Chrisman, 1992). The risk of iatrogenic neurological damage is minimized if CSF can be obtained from the dorsal subarachnoid space rather than the ventral space.

## Sample handling

CSF contains very little protein; this causes the leucocytes that are present to deteriorate rapidly. Ideally, CSF should be either analysed or preserved for analysis within 30-60 minutes of collection to minimize cellular degradation (Taylor, 1998; Parent, 1999; Fenner, 2000). Cell counts can readily be performed in private practice using a haemocytometer. Most CSF samples contain a relatively low concentration of leucocytes; therefore, the samples must be concentrated by some means prior to microscopic examination. For this purpose, commercial laboratories use a cytocentrifuge to concentrate the cells in a single drop of CSF on to a microscope slide. Use of this method renders an average cell retrieval of approximately 15% (Parent, 1999). If sample analysis by a commercial laboratory must be delayed and preservatives will not be used, an in-house sedimentation chamber (Figure 3.14) can be constructed, as described in Figure 3.15. Use of a similarly constructed sedimentation chamber (not pictured) yields a cell retrieval of approximately 25%, though preservation of cellular morphology is diminished compared with cytocentrifugation (Jamison and Lumsden, 1988). The slides that are made using the sedimentation chamber may be either examined in-house or submitted to a commercial laboratory for microscopic evaluation. Other tests, such as protein measurement, or microbial culture, can be performed upon the remaining CSF sample.



Spinal fluid sedimentation chamber. The apparatus was constructed from a microscope slide, a piece of filter paper with a hole punched in the centre, the barrel of a 1 ml syringe and two binder clips. The second hole in the filter paper is present for illustration. In the functioning chamber, the only hole needed is directly under the barrel of the syringe.

### Materials

Standard hole puncher
Two binder-type paper clips
Filter paper
Clean, glass microscope slide
1 ml syringe, plunger removed, cut in half

#### Method

- 1. Make a hole in the filter paper using the hole puncher.
- 2. Place the filter paper on top of the microscope slide.
- Centre the flanged end of the syringe barrel (the end where the plunger would be inserted) directly over the hole in the filter paper.
- Clamp the flanges of the syringe barrel on to the microscope slide using the two binder paper clips.
- Load 0.25–0.5 ml of CSF into the open end of the barrel. The fluid will diffuse out of the bottom of the syringe into the filter paper, leaving the cells to stick to the glass underneath the hole in the filter paper.
- 6. Allow the fluid to diffuse for 30 minutes.
- Air-dry the slide; heat fixing is unnecessary and may damage the cells resulting in poor preservation for cytological examination.
- Stain the slide with a Romanowsky-type stain (e.g. Wright– Giemsa) or send it to a cytopathologist for staining and interpretation, if desired.

3.15 Materials and method for in-house sedimentation chamber assembly.

Alternatively, prior to shipment to a commercial laboratory for analysis, CSF samples can be preserved by refrigeration and the addition of one drop of buffered 10% formalin or one drop of autologous serum to 0.25 ml of CSF (Bienzle *et al.*, 2000). The addition of autologous serum will preserve the CSF leucocytes for up to 24–48 hours after collection, but will falsely elevate the total protein content. If this option is elected, a second CSF aliquot without the added serum should also be submitted for microprotein determination. Preservation with formalin does not affect the microprotein assay.

# Sample analysis

Results of CSF analysis can rapidly provide information that may be useful in selecting treatment protocols, prognosis or dictating further diagnostic tests (e.g. serology, microbiology). However, the results may be normal even in the presence of significant CNS disease. Furthermore, only occasionally will CSF analysis alone yield a definitive clinical diagnosis. CSF findings need to be interpreted in the light of historical information, clinical signs and other diagnostics. Figure 3.16 gives an overview of the components of CSF analysis and normal findings.

Characteristic	Normal findings	
Assessment of gross physical characteristics: colour and clarity	Colourless and transparent	
Microprotein concentration	AO: <25 mg/dl Lumbar: <40 mg/dl	
Cell counts	RBC: 0/μl (excluding iatrogenic blood contamination) WBC: <5/μl	
Cytology and differential leucocyte count	Lymphocytes: 60–70% Monocytes: 30–40% Neutrophils: <1% (excluding iatrogenic blood contamination) Eosinophils: <1% Ependymal lining cells: rare	

Components of CSF analysis and normal findings.

# Gross physical characteristics

Normal CSF is colourless. CSF may be coloured by the addition of cells or cellular breakdown products (Figure 3.17). When CSF is discoloured, it is often either red or yellow-orange (xanthochromic). When it is red, it is necessary to determine whether iatrogenic or pathological haemorrhage has occurred. This distinction is made possible by gross and microscopic observation. Pathological haemorrhage may be suspected if the sample is uniformly red during collection, whereas blood contamination due to iatrogenic haemorrhage is suggested if the sample is initially colourless but becomes red-tinged during collection. When placed in a tube that does not contain anticoagulant, a moderately

Colour	Significance Signi		
Red	latrogenic haemorrhage (blood contamination) Pathological haemorrhage		
Yellow-orange (xanthochromia)	Bilirubin associated with chronic pathological haemorrhage (RBC breakdown) Bilirubin associated with hyperbilirubinaemia or disrupted blood–brain barrier		
Yellow-green	Markedly increased nucleated cell concentration (e.g. purulent inflammation; neoplasia, rarely)		
Grey-black	Presence of melanin granules or melanocytes		

3.17 Abnormal CSF colours and their aetiologies.

to severely blood-contaminated sample is likely to clot. Additionally, an aliquot of red CSF can be centrifuged. A xanthochromic supernatant indicates that pathological haemorrhage has probably occurred; a colourless supernatant suggests that contamination due to iatrogenic haemorrhage has occurred. The microscopic differences between pathological and iatrogenic haemorrhage are detailed below.

The presence of bilirubin in CSF imparts xanthochromia. When present, xanthochromia is most commonly due to chronic haemorrhage. Erythrocytes that enter the CSF due to haemorrhage are metabolized, resulting in bilirubin formation. Less commonly, when the serum concentration is markedly increased, conjugated bilirubin may cross the blood—brain barrier. Conjugated and unconjugated bilirubin can cross a damaged blood—brain barrier.

Yellow-green or grey-black CSF is observed uncommonly. Yellow-green discoloration can be caused by a high nucleated cell count, as seen with purulent inflammation (e.g. septic meningitis) or a neoplastic infiltration. Melanin granules or melanocytes are a rare abnormal finding in the CSF. If present at a sufficient concentration, as is occasionally seen with CNS melanoma, they may engender a grey discoloration (Paradis, 1998).

Normal CSF is transparent or clear. It is made cloudy when the number of leucocytes is markedly increased above 500 white blood cells (WBC)/ $\mu$ l. Since the cell count must be substantially increased before CSF becomes cloudy, estimation of the cell count based on gross examination is of minimal utility. It is necessary to perform a manual cell count using a haemocytometer to detect mild or moderate leucocyte elevations above the normal leucocyte count of <5 WBC/ $\mu$ l.

## Microprotein determination

The cranial-to-caudal flow of CSF normally results in a protein concentration differential between samples collected from the AO and lumbar sites. The protein concentration is normally higher in samples collected from the lumbar site than those collected from the AO site. This difference can be increased when CNS disease is present, especially when the spinal cord is involved. The CSF protein concentration is far less than that in other body fluids and cannot be measured by a refractometer. Precise microprotein quantitation is performed spectrophotometrically using reagents that are typically found only in commercial laboratories. The normal protein concentration depends upon the species of the patient, the site of sample collection and the method used to measure the protein. Results are best interpreted using a reference range established by the individual laboratory measuring the microprotein concentration. In general, canine and feline CSF collected from the AO site contains <25 mg protein/dl and that from the lumbar site contains <40 mg protein/dl. The microprotein concentration can be estimated using a protein dipstick or the protein pad of a urine dipstick (Jacobs et al., 1990). The protein dipstick reaction results in a colour change that is interpreted in ranges indicated in Figure 3.18. Potential causes for increased microprotein concentration are discussed below.

<30 mg/dl	30 mg/dl	100 mg/dl	300 mg/dl	>2000 mg/dl
Trace	1+	2+	3+	4+

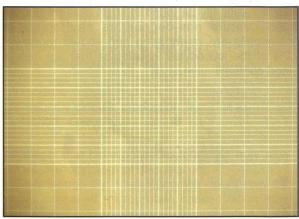
3.18

Protein dipstick interpretation ranges.

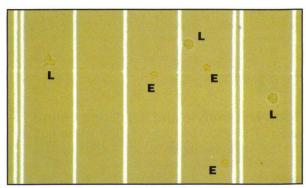
# Total erythrocyte and leucocyte counts

Normal CSF should contain no erythrocytes, but a low number of erythrocytes is commonly seen due to iatrogenic blood contamination. Also, erythrocytes may be seen with pathological haemorrhage. Most evaluators consider <5 WBC/µl to be normal for all species. An increased number of CSF leucocytes is referred to as pleocytosis. A pleocytosis is further characterized during microscopic examination and differential cell count based upon the predominant leucocyte(s).

The erythrocyte and leucocyte counts are measured by placing undiluted CSF into both chambers of a haemocytometer. The cell counts are performed after the cells have settled within the haemocytometer chambers, which is accomplished by allowing the haemocytometer to sit within a humidified Petri dish for 5 minutes before counting the cells. Each chamber contains nine large squares (Figure 3.19). The number of leucocytes and erythrocytes in the centre square and the four corner squares of both chambers (five squares per chamber x two chambers = 10 squares) are counted to get the total leucocyte and erythrocyte counts per microlitre. If an excessive number of erythrocytes are present, only one large square should be counted and the number should be multiplied by 10 to get the total erythrocyte count per microlitre. Care must be taken to distinguish leucocytes from any erythrocytes present (Figure 3.20).



Haemocytometer grid. This photomicrograph depicts the grid in one of the two chambers present. Each grid is divided into 9 large squares, which are further subdivided and will be described here for the purpose of observer orientation. The large centre square is divided into 256 smaller squares. Each of the four large corner squares is divided into 16 smaller squares (outside rows not pictured here). The cells within the large centre grid square and the four large corner grid squares from both chambers are counted (a total of 10 large squares). The total cell counts, expressed as the number of cells per microlitre, are equal to the sum of all cells counted in the 10 large grid squares from both haemocytometer chambers.

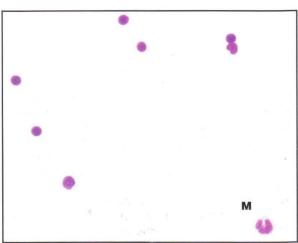


RBCs and WBCs within fluid in a haemocytometer chamber. Three erythrocytes (E; smaller, light orange cells) and three leucocytes (L; larger, stippled cells) are shown in this photomicrograph. Original magnification X125.

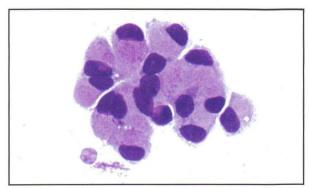
- Erythrocytes are small, biconcave, light orange and very translucent; they may also be crenated.
- Leucocytes are larger, have a stippled appearance, are greyish and are less translucent than erythrocytes.

# Cytology and differential leucocyte count

Microscopic examination is usually performed on concentrated CSF samples stained with Romanowskytype stain. In normal CSF, mononuclear cells predominate (Figure 3.21). Small, well differentiated lymphocytes typically comprise 60-70% of the differential cell count; minimally vacuolated, large mononuclear phagocytes frequently comprise 30-40%. The background is usually colourless and may contain a low number of erythrocytes, a small amount of stain precipitate and rare keratinized, squamous epithelial cell contaminants. Ependymal lining cells may occasionally be found in small clusters (Figure 3.22). Mature non-degenerate neutrophils or eosinophils are rarely seen and should represent <2% of the leucocytes in samples that are free of blood contamination.



Spinal fluid from a dog. Seven small well differentiated lymphocytes and one minimally vacuolated large mononuclear phagocyte (M) are seen. Wright-Giemsa stain; original magnification X125.



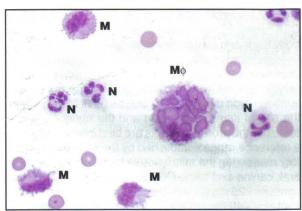
Cluster of ependymal cells from canine spinal fluid. Note the eccentrically located nuclei and the central accumulation of eosinophilic granular material in the basophilic cytoplasm. Wright–Giemsa stain; original magnification X250.

# Distinction of pathological and iatrogenic haemorrhage

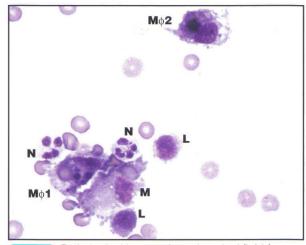
If erythrophagia, haemosiderophages or haematoidin crystals are observed during microscopic examination, pathological haemorrhage is suggested (Figures 3.23 and 3.24).

- Erythrophagia denotes reactive mononuclear phagocyte ingestion of erythrocytes, which are observed within the phagocyte's cytoplasm.
- Haemosiderophages are reactive mononuclear phagocytes that contain variably sized, round to oval particles of dark blue-green haemosiderin pigment, which stain positively for iron with Prussian blue. The iron is derived from metabolized haemoglobin.
- Bilirubin is another product of haemoglobin metabolism; it forms golden, rhomboid or rectangular haematoidin crystals.

latrogenic blood contamination is indicated by the presence of platelets and/or the absence of erythrophagia or erythrocyte breakdown pigments (haemosiderin, haematoidin).



Pathological haemorrhage in spinal fluid from a dog. A large macrophage (M\$\phi\$) contains several phagocytosed erythrocytes, indicative of acute or recent haemorrhage. Three other large mononuclear cells (M), three non-degenerate neutrophils (N) and extracellular erythrocytes are also present. Wright–Giemsa stain; original magnification X250.



Pathological haemorrhage in spinal fluid from a dog. A macrophage (M\phi1) contains phagocytosed erythrocytes and dark blue-green haemosiderin. A second macrophage (M\phi2) contains haemosiderin and golden rhomboid haematoidin crystals. The presence of haemosiderin and haematoidin indicates chronic haemorrhage. One other large mononuclear cell (M) exhibiting erythrophagia, two lymphocytes (L), two non-degenerate neutrophils (N) and extracellular erythrocytes are also present. Wright–Giemsa stain; original magnification X250.

# Interpretation of CSF analysis

### Effects of blood contamination

latrogenic contamination of the CSF sample with peripheral blood may falsely increase the protein concentration, leucocyte count and relative percentage of neutrophils. Even when samples are contaminated with blood, analysis may still be useful as cellular abnormalities may be detected during microscopic examination. When the blood contamination is mild (<5000 RBC/µl), two correction formulae may be used to get a very rough estimate of what the protein concentration and leucocyte count would be if the contamination were absent.

- Protein concentration correction formula: for every 1000 RBC/μl, the protein concentration can be adjusted down by 1 mg/dl.
- Leucocyte count correction formula: for every 500 RBC/µl, the leucocyte count can be adjusted down by 1 WBC/µl.

Some reports suggest that these formulae are inaccurate and that mild to moderate blood contamination up to 13,200 RBC/ $\mu$ l does not significantly affect the CSF protein concentration and leucocyte count (Hurtt and Smith, 1997; Wilson and Stevens, 1977). Information derived from these formulae is interpreted most effectively when clinical signs and results of microscopic examination are also considered.

## **Abnormal CSF findings**

Figure 3.25 lists potential abnormal CSF analysis findings.

Increased microprotein concentration with normal total cell count: Albuminocytological dissociation occurs with various diseases that alter the

# Increased microprotein concentration with normal total leucocyte count (albuminocytological dissociation)

Normal differential leucocyte count Increased neutrophil percentage

# Pleocytosis (usually occurs with concurrently increased protein concentration)

Lymphocytic Mixed cell Neutrophilic Eosinophilic

## Other microscopic findings

Infectious agents Evidence of:

Myelin degeneration Pathological haemorrhage

Neoplasia

Degenerative disease Sample contamination

2 25

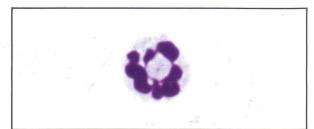
Potential abnormal CSF analysis findings.

blood-brain barrier and allow protein from the blood circulation to enter the CNS, increase the production of protein within the CNS or obstruct the flow of fluid and therefore protein within the CNS. Considerations include:

- An extradural compressive lesion, e.g. intervertebral disc disease (IVDD), cervical stenotic myelopathy, spinal synovial cyst, vertebral osseous lesions, neoplasia
- An intramedullary mass effect, e.g. neoplasia, syringo- or hydromyelia, protozoal granuloma
- · Degenerative myelopathy
- Ischaemic CNS necrosis, e.g. due to fibrocartilaginous embolus
- Trauma
- Vasculitis
- Intrathecal globulin production, e.g. due to infection or neoplasia.

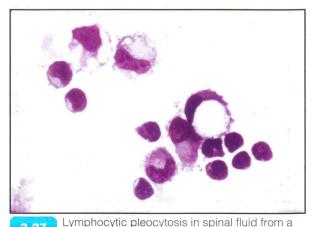
Patients that have polyradiculoneuritis may also have albuminocytological dissociation.

Even though the total leucocyte count may be normal, increased microprotein concentration may be associated with an abnormal cell population, such as an increased percentage of neutrophils. This can occur with CNS disease that does not involve the meninges or ependymal cells, such as a vertebral fracture, cervical stenotic myelopathy, IVDD and severe seizure activity. These findings may also be seen with inflammatory CNS diseases if the total CSF leucocyte count has been reduced iatrogenically by treatment with glucocorticoids or antibiotics prior to sample collection. Previous glucocorticoid administration may be suspected if hypersegmented neutrophils (more than five nuclear lobulations) are observed in the CSF (Figure 3.26).

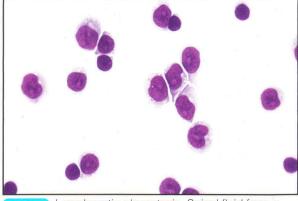


3.26 Spinal fluid from a dog previously given glucocorticoid therapy. A hypersegmented neutrophil is seen. The nucleus is hyperchromic and has more than five lobulations. Wright–Giemsa stain; original magnification X250.

Lymphocytic pleocytosis: With a lymphocytic pleocytosis (Figure 3.27) the CSF protein concentration is typically increased and the leucocyte count is >5 WBCs per microlitre with >50% lymphocytes. This finding may be seen with a number of different disease conditions but is most commonly associated with viral meningitis. In dogs, this includes rabies and canine distemper virus. Pugs, Maltese, Yorkshire Terriers and possibly other toy breeds may develop a severe necrotizing, non-suppurative meningoencephalitis, originally called 'Pug dog encephalitis'. This class of disease is associated with a moderate to marked pleocytosis, which is typically lymphocytic, although a mixed cell pleocytosis can be seen. Feline polioencephalomyelitis, an uncommon disease of 2- to 3-month-old cats, may also be associated with lymphocytic meningitis and pleocytosis. CNS lymphoma can cause a lymphocytic pleocytosis in any species. The lymphocytes may appear atypical (lymphoblasts) (Figure 3.28) or well differentiated, which occurs more frequently in cats than in dogs with lymphoma. Additionally, feline lymphoma is usually extradural; therefore, neoplastic cells may not be found in the CSF. Although typically associated with mixed cell pleocytosis, animals with toxoplasmosis, neosporosis, ehrlichiosis or granulomatous meningoencephalitis (GME) may present with a lymphocytic pleocytosis. Steroid-responsive meningitis should be considered, although it typically causes neutrophilic pleocytosis.

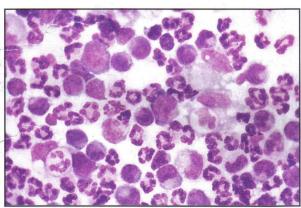


Pug. Several small, well differentiated lymphocytes are seen. Five macrophages, some of which are reactive with marked cytoplasmic vacuolation, are also seen. Wright–Giemsa stain; original magnification X250.



3.28 Lymphocytic pleocytosis. Spinal fluid from a dog with spinal lymphoma. Several large immature lymphoblasts are seen. Note the diffuse chromatin pattern and distinct pale nucleoli in the neoplastic lymphocytes. A low number of small non-neoplastic lymphocytes with dark condensed nuclear chromatin are also seen. Wright–Giemsa stain; original magnification X250.

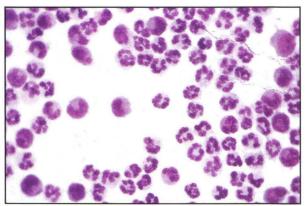
Mixed cell pleocytosis: With a mixed cell pleocytosis the CSF protein concentration is typically increased and the leucocyte count is >5 WBC/µl. The predominant population of nucleated cells is a mixture of lymphocytes and large mononuclear phagocytes, with a variable number of neutrophils. A lesser number of plasma cells and rare eosinophils may also be present. The classic example of a mixed cell pleocytosis occurs with canine GME (Figure 3.29). Other diseases that can cause a mixed cell pleocytosis are: fungal infections (e.g. cryptococcosis, blastomycosis and aspergillosis); some rickettsial infections, such as ehrlichiosis or Rocky Mountain spotted fever (RMSF); and protozoal or algal infections, such as toxoplasmosis, neosporosis and protothecosis. Additionally in dogs, when other possibilities are eliminated, steroid-responsive meningitis should always be considered, due to the variable cytological appearance associated with this disease. In cats, neurological disease associated with chronic feline infectious peritonitis (FIP) may present with a mixed cell pleocytosis, though in many



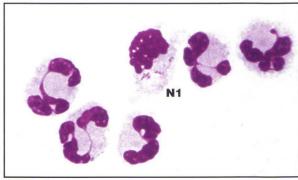
3.29 Mixed cell pleocytosis. Spinal fluid from a dog with granulomatous meningoencephalitis (GME). A mixture of large macrophages, non-degenerate neutrophils and small lymphocytes is seen. Wright–Giemsa stain; original magnification X250.

cases there may be a neutrophilic predominance. Most of the above conditions typically result in a moderate to severe pleocytosis (50–500 WBC/ $\mu$ l). Mild mixed cell pleocytosis (<50 WBC/ $\mu$ l) can also be seen with any condition that results in CNS infarction or myelomalacia (e.g. acute intervertebral disc herniation) (Chrisman, 1992).

Neutrophilic pleocytosis: With a neutrophilic pleocytosis (Figure 3.30) the CSF protein concentration is typically increased and the leucocyte count is >5 WBC/ul with neutrophilic predominance. The presence of a neutrophilic pleocytosis should alert the clinician to the possibility of bacterial or, less commonly, fungal meningitis. Culture of CSF should be considered for animals with a neutrophilic pleocytosis, especially those that have other signs suggestive of bacterial meningitis, such as pyrexia, peripheral neutrophilia with or without left shift and/or toxic change, and degenerative change of CSF neutrophils. Degenerative change is not present in all cases of bacterial meningitis (e.g. due to prior antimicrobial administration or infection by a bacterium producing few cytotoxic substances). The presence of degenerative change in CSF neutrophils should not be used as the sole criterion to determine whether or not a CSF sample should be cultured; it is prudent to integrate other clinical information when making this decision. Cytologically, a definitive diagnosis of sepsis can be made by finding intracellular bacteria within the cytoplasm of degenerative neutrophils (Figure 3.31). In dogs, the classic example and most common cause of neutrophilic pleocytosis is steroidresponsive meningitis. With this disease, the leucocyte count is usually >50 WBC/µI, the neutrophils are non-degenerate and bacterial cultures are negative. Other causes of neutrophilic pleocytosis in the dog include RMSF and steroid-responsive meningitisarteritis in Beagles, Bernese Mountain Dogs, Boxers, German Wirehaired Pointers and other breeds. In cats, FIP is highly likely in those <4 years old with >200 mg protein/dl, >100 WBC/µl and >50% neutrophils in their CSF (Rand et al., 1994). In both



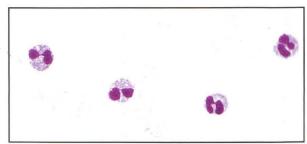
3,30 Neutrophilic pleocytosis. Spinal fluid from a dog with steroid-responsive meningoencephalomyelitis. Mature non-degenerate neutrophils are the predominant nucleated cell type. A lesser number of larger macrophages are also seen. Wright–Giemsa stain; original magnification X250.



3.31 Neutrophilic pleocytosis. Spinal fluid from a dog with bacterial meningitis. Mildly degenerate neutrophils are seen. The neutrophil N1 contains several small pleomorphic rod-shaped bacteria within phagocytic cytoplasmic vacuoles. *Corynebacterium* sp. was cultured from the spinal fluid. Wright–Giemsa stain; original magnification X500.

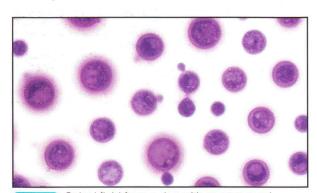
cats and dogs severe seizures, or any disease that produces an area of CNS necrosis, can cause a mild neutrophilic pleocytosis or increased neutrophil percentage with normal cell count. In addition, although neoplastic meningeal cells are rarely observed in the spinal fluid, meningiomas are commonly associated with a neutrophilic pleocytosis. Contrast medium injected during myelography may also induce a transient neutrophilic pleocytosis.

Eosinophilic pleocytosis: With an eosinophilic pleocytosis (Figure 3.32) the CSF protein concentration is typically increased and the leucocyte count is >5 WBC/µl with eosinophilic predominance. A steroid-responsive meningitis associated with a large number of eosinophils has been reported in both dogs and cats. Golden Retrievers are over-represented (Smith-Maxie et al., 1989). This is an uncommon disease, which is associated with a severe pleocytosis and >80% eosinophils. Eosinophilic pleocytosis has also been reported with aberrant parasitic migration, toxoplasmosis, neosporosis, cryptococcosis, protothecosis, neoplasia (e.g. T cell lymphoma) and, very rarely, with rabies and canine distemper (Chrisman, 1992). Therefore, these infections should be excluded using serum or CSF serology prior to glucocorticoid administration.

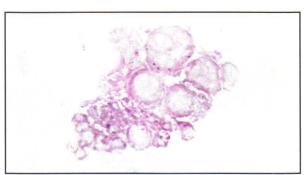


3.32 Eosinophilic pleocytosis. Spinal fluid from a Golden Retriever with eosinophilic steroid-responsive meningoencephalomyelitis (SRM). Numerous eosinophils are seen in this unconcentrated spinal fluid that had 21,000 WBC/μl. Wright–Giemsa stain; original magnification X250.

Other microscopic findings: Infectious agents such as bacteria, fungi or (rarely) protozoa may be identified (Figures 3.31 and 3.33). With acute distemper viraemia, round to oval inclusions are identified rarely in CSF leucocytes (see Figure 3.6). Myelin degeneration can be seen with canine degenerative myelopathy or with any disease that causes myelin breakdown. Cytologically, free myelin appears as loose aggregates of circular, pale pink to grey material (Figure 3.34). Pathological haemorrhage may be noted with infectious, inflammatory, traumatic and neoplastic diseases (see Figures 3.23 and 3.24). Most CNS neoplasms are typically poorly exfoliative; therefore, neoplastic cells are rarely identified in the CSF. CNS lymphoma is an exception; it can be associated with a moderate to severe lymphocytic pleocytosis. Typically, a significant portion of the lymphocytes are immature blasts (see Figure 3.28). However, blasts will not be observed when the neoplastic lymphocytes are well differentiated or when the tumour is extradural, as occurs often in feline lymphoma. With lysosomal storage diseases, large round, oval or linear inclusions may be identified uncommonly in CSF mononuclear cells (see Figure 3.3). Sample contaminants may be observed, such as keratinized, squamous epithelial cells or those that may occur during collection, including haematopoietic cells from the bone marrow (Christopher, 1992) and CNS elements, such as myelin (Figure 3.34), meningeal cells, ependymal cells (see Figure 3.22) and neuron cell bodies.



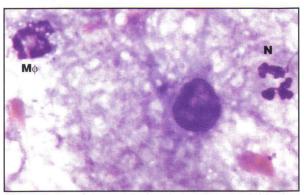
3,33 Spinal fluid from a dog with cryptococcal meningitis. Numerous large encapsulated yeasts, some of which are budding, are seen. Cryptococcus neoformans was cultured from the fluid. New methylene blue stain; original magnification X250.



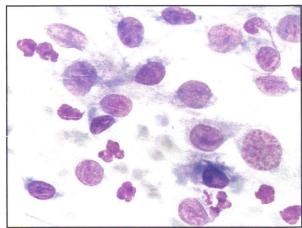
3.34 Spinal fluid containing free myelin. A loose aggregate of circular pink myelin is seen in the spinal fluid from an aged German Shepherd Dog with a presumptive diagnosis of degenerative myelopathy. Wright-Giemsa stain; original magnification X250.

# Fine needle aspiration and imprint cytology

Fine needle aspiration and biopsy imprint cytology can be used to evaluate masses within the CNS (see Chapter 6). Fine needle aspiration cytology is most effective when samples are collected using ultrasonography or computed tomography (CT) guidance. CNS cytology can provide a rapid, economical and (when obtained by aspiration) minimally invasive technique to distinguish inflammatory lesions (Figure 3.35) from neoplastic lesions (Figure 3.36). In one study (Platt et al., 2002), cytology correctly identified lesions as neoplastic with 100% accuracy but histology was required to determine the specific tumour type. Cytology identified the cell origin of the tumour with 90% accuracy. The cytological diagnosis of the exact tumour type correlated with 50% of the histological diagnoses for samples obtained by needle biopsy and with 60% of those obtained from necropsy specimens.



Tissue imprint from a dog with granulomatous meningoencephalomyelitis (GME). A large neuron is seen in the centre of the photomicrograph. A single non-degenerate neutrophil (N) and macrophage (Mφ) are also present. Wright–Giemsa stain; original magnification X250.



Tissue imprint from a dog with a meningioma, showing many neoplastic meningeal cells. The cytoplasm of these cells is lightly basophilic, spindle-shaped and extremely wispy. The nuclei have malignant features, such as anisokaryosis (variable nuclear size), coarse chromatin pattern and occasional prominent large nucleoli. Wright–Giemsa stain; original magnification X250.

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# **Electrophysiology**

# Luc Poncelet

## Introduction

Electrophysiological studies record electrical activity from muscles or neural structures as a function of time. This activity can be spontaneous as in electroencephalography (EEG) or electromyography (EMG), or it may be the consequence of stimulation as in nerve conduction velocity (NCV) measurements and evoked potential studies.

Electrophysiological studies evaluate neural tissue, the neuromuscular junction and muscle function. As such, they form a functional follow-up diagnostic modality to the neurological examination that can be used to confirm, refine and quantify the clinical findings. Electrophysiological methods are minimally invasive but require sedation and frequently anaesthesia. The cost of the equipment and the experience needed for conducting these studies limit their use to academic and referral clinics.

Electrophysiological studies provide immediate and objective data but are rarely diagnostic of a specific disorder. Confirming the nature of lesions requires other diagnostic modalities such as imaging or tissue biopsies (see Chapters 5 and 6). Nevertheless, just as the functional information gathered from the neurological examination allows broad localization of the lesion and estimation of its severity (see Chapter 2), electrophysiological studies can confirm and refine this lesion localization and quantify its severity. In addition, indirect conclusions about the lesion type can often be drawn. For example, the results of motor nerve conduction studies provide information on whether the pathology is primarily affecting the myelin sheath or the axon. EEG patterns can also suggest a lesion type.

Electrophysiological investigations can address the efferent or afferent nervous system and can focus on either the peripheral or central components (Figure 4.1). Finally, the special senses and the cerebral cortex can be evaluated.

From a functional point of view, the peripheral components include the neuronal cell bodies in the spinal cord intumescences, brainstem or ganglia, and the nerve roots in addition to their respective peripheral nerves.

# Efferent system

Efferent (motor) system investigation records electrical activity from the effectors of the system (the muscles) after stimulation of nervous tissue at various points in the peripheral and central nervous systems.

- The peripheral components are investigated by stimulating peripheral nerves for the motor nerve conduction velocity (MNCV), repetitive stimulation (RS) and F wave studies.
- Spontaneous electrical activities in muscles are recorded during EMG and form an important adjunct. Single fibre EMG is a specialized test used to evaluate single myofibres in neuromuscular junctional disease.
- The central efferent pathways have been investigated by magnetic or electrical stimulation of the brain and spinal cord (Sylvester et al., 1992; Van Ham et al., 1996) but these methods have not reached routine clinical use and will not be described in this chapter.

Nervous system			10 " " "		
Somatic afferent (sensory)		Special senses	Somatic efferent (motor)		
Peripheral	Central (+ peripheral) <sup>a</sup>		Peripheral	Central (+ peripheral)*	
SNCV Mixed NCV (+motor fibres) * Reflex studies (+efferent arm) *	SSEP	BAEP ERG <sup>b</sup> VEP <sup>c</sup>	Motor NCV F wave studies RS EMG (+ muscles)*	Magnetic brain stimulation <sup>8</sup>	

Overview of electrophysiological tests. Note that EEG reflects input-output activity of the cerebral cortex and thus cannot be included here. 

May need to be assessed separately. 
Not discussed in this Chapter. 
BAEP = brainstem auditory evoked potential; EEG = electroencephalography; EMG = electromyography; ERG = electroretinogram; NCV = nerve conduction velocity; RS = repetitive stimulations; SNCV = sensory nerve conduction velocity; SSEP = somatosensory evoked potential; VEP = visual evoked potential.

# Afferent somatic pathways

Afferent (sensory) somatic pathways can be investigated by stimulating peripheral nerves.

- The peripheral afferent system is evaluated using sensory (SNC) and mixed nerve conduction velocity studies where recordings are obtained from nerves rather than muscles. Provided the efferent (motor) arm is found to be normal, H-reflex testing can also be used to investigate peripheral afferent fibres.
- The central nervous system (CNS) is evaluated through somatosensory evoked potentials (SSEPs) that can be recorded at the level of the spine or skull.

# Special sensory systems

Special sensory systems can be studied by evoked potentials. The most widely used method is the brainstem auditory evoked potentials (BAEPs) recording (also known as brainstem auditory evoked responses, BAERs) obtained in response to auditory stimuli. This is used to investigate auditory function and to assess the functional integrity of the brainstem.

## Cerebral cortex

The cerebral cortex can be evaluated with EEG. This technique records spontaneous activity coming mostly from the grouped activity in the apical dendrites of cortical neurons.

The diagnostic value of these methods is well established and their indications and usefulness will be considered in this Chapter.

# Types of recorded potentials

Two types of potential may contribute to the recorded potentials: the compound action potential and the field potential. Field potentials should further be divided into near and far field potentials (Figure 4.2).

## Compound action potentials

Compound action potentials (CAPs) represent the summation of action potentials travelling along muscle

or neuron fibres. Each contribution to the potential originates from an action potential (depolarization followed by repolarization) approaching, passing by, and running distant from the recording electrode. Examples of CAPs include:

- · Voluntary and evoked muscle potentials
- Evoked nerve potentials
- Somatosensory evoked ascending potentials.

In contrast, spontaneous muscle activities are most often single fibre action potentials. CAPs in the normal patient display a variable latency depending on the distance between the stimulation and recording points but a relatively constant amplitude and waveform. Pathology alters the latency, amplitude and waveform.

# Field potentials

## Near field potentials

Near field potentials originate from potentials within cell bodies and processes of neuron groups in close approximation to the recording needle. They result from the synchronous activity of synapses. Each contribution is small and its amplitude diminishes quickly with distance. Being locally generated, near field potentials characteristically display a constant latency independent of the recording electrode location and an exponentially decreasing amplitude when the recording electrode is moved away from the potential generating structure. Neuron processes involved in the generation of such potentials should all run towards or away from the recording electrode to record a potential from a distance. Should these neuron processes run in a perpendicular direction or radiate in all directions, no potential would be recorded. Somatosensory cord dorsum, medullary potentials and EEG potentials are mostly made of near field potentials.

# Far field potentials

Far field potentials result from the lack of homogeneity of the nervous tissue in which action potentials are travelling. Changes in the conductivity of the medium, the volume conductor size or the direction of the nerve fibres are the most common causes of far field potentials.

		Amplitude range	Origin	Source	Amplitude fct of distance <sup>a</sup>	Latency fct of distance a	Examples
CAP	Muscle	mV	Travelling action potentials	Moving	Almost constant	Increases	CMAP
	Nervous fibre	μV	Travelling action potentials	Moving	Almost constant	Increases	CNAP AEP
Field potential	Near	μV	Currents caused by synaptic activity	Fixed	Exponential decrease	Constant	CDP EEG
	Far	μV	Anisotropy of the volume conductor	Fixed	Recordable from long distances	Constant	Some peaks of the BAEP

Characteristics of recorded potentials. <sup>a</sup> Fct of distance = as a function of the distance from the generator (fixed source) or from the stimulation point (moving source). AEP = ascending (somatosensory) evoked potential; BAEP = brainstem auditory evoked potential; CAP = compound action potential; CDP = cord dorsum potential; CMAP = compound muscle action potential; CNAP = compound nerve action potential; EEG = electroencephalography.

For example, at the location where a nerve root enters the spinal cord, the surrounding tissue conductivity changes (i.e. due to epidural fat/cerebrospinal fluid), the volume conductor size changes (root/spinal cord) and the direction of the fibres change (ascending branches of the primary afferents). Far field potentials also display a constant latency but can sometimes be recorded from surprisingly long distances. Most of the BAEP waves are made of far field potentials.

# **Evaluation of the peripheral motor system**

Neuromuscular weakness is the main indication for these tests once circulatory, respiratory and metabolic aetiologies have been ruled out (see Chapter 17). Weakness may be of neural, neuromuscular junction or muscular origin. In the first hypotonia and hyporeflexia are usually observed clinically.

Five procedures are of use for the evaluation of the peripheral motor system:

- EMG
- MNCV
- F wave evaluation
- · Repetitive motor nerve stimulation
- Single fibre EMG.

These tests are usually conducted under general anaesthesia because the animal's muscles must be relaxed in order to detect spontaneous activity and because nerve stimulation is painful. Voluntary motor activity can also be investigated but since this requires the collaboration of awake patients it is seldom used in dogs or cats.

## Electromyography

## **Indications**

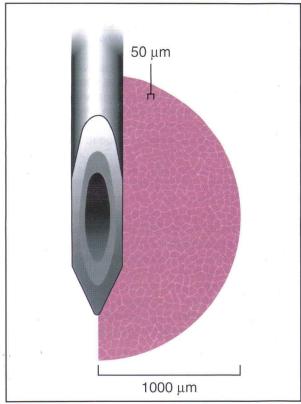
EMG is used to identify denervated muscles and to identify and characterize myopathies.

## **Technique**

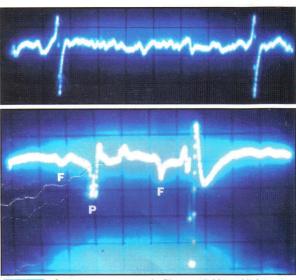
In EMG, muscles are explored with a concentric needle electrode that samples electrical activity in a small muscle volume at its tip (Figure 4.3). Nearly all striated muscles can be probed including: limb, masticatory, facial, laryngeal, pharyngeal, paraspinal, tail and anal sphincter muscles. A fairly extensive and accurate map of abnormal muscles can be built within a reasonable time (Griffiths and Duncan, 1978; Brown and Zaki, 1979; Farnbach, 1980; Van Ness, 1986a).

## Normal findings

A normal relaxed muscle is electrically silent except in the endplate region where endplate noise due to miniature endplate potentials and endplate spikes, thought to be caused by the presence of the electrode near the endplate, are recorded (Figure 4.4). During concentric needle electrode movements mechanical triggering of muscle fibre potentials generates insertion potentials. The examiner should be familiar with



Relative sizes of the concentric needle electrode and the muscle fibre. The amplitude of the electrode potential decreases exponentially with distance, the electrode is not influenced by muscle fibres nore than 1000 µm from its tip. The larger the recording electrode surface, the smaller the potential decay as a function of the distance – non-insulated needles or surface electrodes (alligator clip) give a more comprehensive picture of the underlying muscle activity.



Spontaneous muscle fibre activities. An intact relaxed normal muscle is electrically silent except in the endplate area where endplate noise and spikes are found (upper tracing). In a denervated muscle spontaneous electrical activities, like fibrillation potentials (F) and postivie sharp waves (P), may be recorded at various locations. Vertical: 50 μV/div; horizontal: 2 ms/div (upper tracing), 5 ms/div (lower tracing); positivity downwards. (Copyright L. Poncelet)

the aspects of these normal findings related to random neurotransmitter release at the neuromuscular junction level and muscle fibre mechanical stimulation. By inserting the needle electrode to different depths and in different places a large volume of muscle can be explored.

## **Abnormal findings**

Five to ten days after a peripheral motor nerve lesion (after the time needed for the degeneration of the distal axonal segment) denervated muscle fibres exhibit spontaneous depolarizations that are most often recorded in the form of fibrillation potentials and positive sharp waves (see Figure 4.4).

Multifocal muscle disease can isolate parts of muscle fibres from their endplate region and these isolated parts may exhibit spontaneous electrical activity. In case of severe and long-standing neuromuscular junction blockade, such as is sometimes seen in myasthenia gravis, spontaneous activities may occasionally be recorded.

More complex spontaneous activities called 'complex repetitive discharges' characterized by an abrupt start and finish are sometimes recorded and can be present in both neuropathic and myopathic disease (Figure 4.5). Myotonic discharges, characterized by waxing and waning amplitude and frequency, are associated with myotonia in dogs.

Spontaneous activities objectively confirm a peripheral nerve or muscular problem and can also infrequently be recorded in junctional problems. EMG

alone is unable to discriminate between these possible localizations and poorly correlates to the severity of the problem. Follow-up nerve conduction studies and frequently muscle and/or nerve biopsies are therefore indicated. Concurrent nerve and muscle lesions can also be encountered.

# Maximum motor nerve conduction velocity

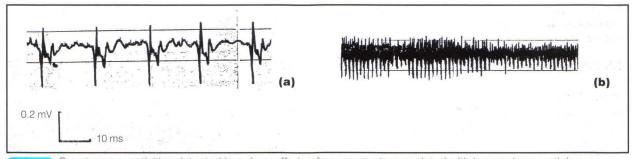
### **Indications**

Motor nerve conduction studies are used to investigate suspected peripheral neuropathies.

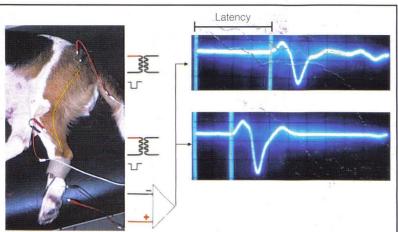
# Technique and findings

MNCV is obtained by stimulating a motor nerve at a minimum of two sites and recording the evoked electrical activity, the compound muscle action potential (CMAP), in one of the target muscles each time (Figure 4.6).

- For the pelvic limb, responses in the plantar interosseous muscles to sciatic-tibial nerve stimulation and responses in the short digital extensor muscles to sciatic-peroneal nerve stimulation are most often used.
- For the thoracic limb, responses in the palmar interosseous muscles to ulnar nerve stimulation are used (Lee and Bowen, 1970; Farnbach, 1980; Nafe and Lee, 1983; Van Ness, 1986 a, b).



Spontaneous activities detected in a dog suffering from myotonia associated with hyperadrenocorticism. (a) Complex repetitive discharges. (b) Slowly waxing activity sometimes called 'pseudomyotonia' (positivity downwards). (Reproduced from Poncelet *et al.*, 1992b, with permission from *The Journal of Small Animal Practice*)



Maximum motor nerve conduction velocity. The sciatictibial nerve is stimulated at a proximal and a distal location and the resulting CMAPs from the plantar interosseous muscles are recorded (left). The latency of the evoked muscle potential measured with the distal stimulation (lower tracing) is subtracted from the latency measured with the proximal stimulation (upper tracing). The distance between the two stimulus locations in mm (yellow path on the left picture) is divided by the latency difference (in ms), giving the maximum MNCV between the two stimulation points (in m/s). Vertical: 2 mV/div; horizontal: 2 ms/div; positivity downwards. (Copyright L. Poncelet)

# Chapter 4 Electrophysiology

A two-location stimulation procedure has also been reported for evaluation of the recurrent laryngeal nerve (Steiss and Marshall, 1988). Expected normal ranges of conduction velocity, CMAP amplitude and duration for each tested nerve, have been published (Lee and Bowen, 1970; Farnback, 1980; Nafe and Lee, 1983; Van Ness, 1986a,b). Target muscle responses to single location stimulation of radial, facial and pudendal nerves are also often recorded.

Effect of patient age (Swallow and Griffiths, 1977; Sims and Redding, 1980) and limb temperature (Lee and Bowen, 1975) on the expected MNCV of specific nerves have been published and should be taken into consideration.

The stimulus is a square electrical pulse, 0.1 ms in duration, with a chosen intensity. It is delivered with a slow repetition rate of 1 or 1.5 Hz. The difference in latency of the CMAP when the nerve is stimulated at two different sites is determined. The resulting latency difference (in ms) is divided by the distance between the two stimulating electrodes (in mm) (see Figure 4.6) and represents the maximum conduction velocity of the motor fibres in the nerve segment between the two stimulating electrodes (in m/s). The amplitude, duration and waveform of the CMAP are also recorded.

Three kinds of changes can be observed (Figure 4.7):

- The CMAP amplitude is severely diminished and the conduction velocity slightly decreased with motor axon loss
- The conduction velocity is severely diminished and CMAP components dispersed with disorders of the myelin sheath

 CMAP to distal stimulation is normal while CMAP to proximal stimulation is altered or suppressed in conduction block resulting from focal demyelination.

In severe lesions a CMAP recording becomes impossible. Mixed patterns of lesions including nerve fibre loss, myelin sheath changes and demyelination are not uncommon. Consequently, clear-cut results only allow reasonable speculation about the lesion type and nerve biopsies are usually performed to characterize the pathology further.

# F waves

### Indications

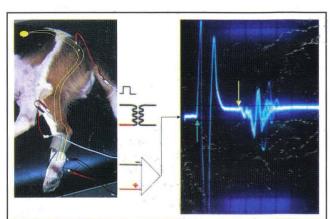
In MNCV studies the nerve segment between the recording electrodes is directly addressed. Although lesions located either at root level or in nerve fibre terminals will affect CMAP recording, other methods are needed to directly confirm such lesions.

# Technique and findings

When motor fibres are stimulated, action potentials travel along the fibres in an *orthodromic* way towards the target muscle and give rise to the CMAP. They also travel in an *antidromic* way towards the nerve cell bodies, causing subsequent depolarization. From time to time, another action potential can be triggered from the axon hillock of the depolarized neuron. These 'backfirings' give rise to the F waves that have a longer latency and a much lower amplitude and duration than the direct CMAP (Figure 4.8). F wave latencies vary

Salida Salas	Distal stimulation			Proximal stimulation			MNCV
	Amplitude	Duration	Latency	Amplitude	Duration	Latency	
Neuron and motor fibre loss	1	N	↑ or N	1 -	N	1 or N	↓ or N
Myelin sheath changes	1	1	1	11	11	11	11
Segmental demyelination	N	N	N	1	1 or N	1 or N	↓ or N

Expected evoked muscle potential changes in peripheral nerve diseases. Note that during the first 10 days after nerve damage, conditions in row 1 can give results similar to those of row 3. These broad indications may also be used for interpreting changes in nerve evoked potentials.  $\downarrow$  = decreased;  $\uparrow$  = increased;  $\mid$  = within normal range.



F wave study. When a motor nerve is stimulated, action potentials travel orthodromically (distal conduction time, green path on the left picture) and trigger the direct muscle response (green arrow on the tracing). They also travel antidromically towards the spinal cord and may induce a backfiring in some motoneurons from the ventral horn cell. A successful backfiring takes 1 ms. These secondary action potentials travel to the target muscle and evoke F waves (yellow arrow on the tracing). The F wave latency represents the conduction time along the yellow path on the left picture and includes the 1 ms backfiring delay. Vertical: 0.2 mV/div; horizontal: 5 ms/div; positivity downwards. (Copyright L. Poncelet)

somewhat depending on the conduction velocity of the backfiring motor fibre. The shortest F wave latency out of at least ten repetitions can be used for nerve root conduction evaluation.

The latency of the direct muscle response (M) represents the conduction time in the distal part of the nerve fibre and in its slower conducting intramuscular branches, plus the time needed for neuromuscular transmission. Two variables are calculated:

- F wave latency
- · F ratio.

Fwave latency: The F wave latency (F) represents the conduction time in the proximal part of the nerve fibre in two directions, the time needed for a successful reflection (1 ms) and the latency of the direct muscle response (M). Consequently, the conduction time in the proximal part of the nerve can be calculated as (F-M-1)/2. Normal values for the ratio of conduction time to limb length are available (Steiss, 1984).

*F ratio:* The ratio of the conduction in the proximal part of the nerve to the distal conduction time is known as the F ratio and is calculated as (F-M-1)/2M.

This ratio increases above normal values in diseases that cause proximal conduction slowing, whilst it decreases below normal values in diseases that cause distal conduction slowing. The F ratio is independent of limb length measurements. Not only does the F ratio explore the proximal part of the nerve but at the same time it is able to detect distal conduction problems (Poncelet and Balligand, 1991). The F ratio has been found most useful in investigating dogs with acute polyradiculoneuritis (Cuddon, 1998).

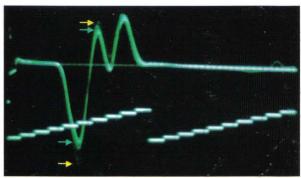
## Repetitive stimulation

## Indications

To investigate patients with suspected myasthenia gravis.

### Technique and findings

The neuromuscular junction can be assessed by repetitive motor nerve stimulations with a repetition rate higher than that used for MNCV measurements (usually 3 to 5 per second). Indeed, the quantity of neurotransmitter delivered at the nerve fibre terminals normally lowers somewhat during such repeated stimulation. However, it always remains above what is needed to efficiently trigger all muscle fibres in a normal subject. This neurotransmitter excess is called the 'safety factor'. Should the number of functional motor plate receptors be diminished, such as in myasthenia, the neurotransmitter quantity would become relatively insufficient. As a consequence action potentials are not triggered in some muscle fibres, which then do not contribute to the CMAP after several stimuli. The amplitude of the CMAP therefore diminishes as the train of stimuli proceeds. A consistent 10% or more decrease in the CMAP amplitude during a train of 10 stimulations at a rate of 3 Hz is suggestive of myasthenia (Figure 4.9) (Malik et al., 1989; Godde and Jaggy, 1993).



4.9 A tracing from a Dachshund with severe myasthenia gravis. Repetitive stimulation of the distal ulnar nerve at 3 Hz and recording from the palmar interosseous muscle. The amplitude of the responses diminishes rapidly as the train of stimuli proceeds and stabilizes at a value 20% lower (green arrows) than that of the first response (yellow arrows); positivity downwards. (Copyright L. Poncelet)

# Single fibre EMG

## Indications

Single fibre EMG is the most sensitive and specific test for myasthenia gravis in people.

## Technique and findings

A fine concentric needle with a side-port close to its tip is used to measure the latency of action potentials following nerve stimulation in individual myofibres. The variation in this latency is called 'jitter' and is usually small. However, in disorders of neuromuscular transmission this variation increases. Due to the technical difficulty of this test it is rarely performed in veterinary medicine but its use in dogs (Hopkins *et al.*, 1993) and cats has been reported, as have normal values in dogs (Añor *et al.*, 2003).

# **Evaluation of the peripheral sensory system**

Evaluation of the afferent component of peripheral nerves is indicated to comprehensively evaluate peripheral neuropathies. It is particularly important when investigating cases with suspected altered or diminished peripheral sensation.

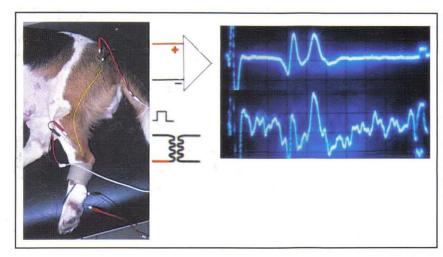
# Maximum sensory nerve conduction velocity

## Indications

Measuring sensory nerve conduction velocity (SNCV) evaluates peripheral afferent fibres and should be completed whenever a peripheral neuropathy is suspected.

## Techniques and findings

Stimuli are delivered to the skin or to a sensory nerve branch and action potentials are recorded proximally from the nerve itself. The conduction velocity is obtained by dividing the response latency by the distance between the stimulating and recording points (Figure 4.10), or by dividing a latency difference by the



Mixed nerve conduction 4.10 velocity as an estimate of the maximum sensory nerve conduction velocity. The tibial nerve is stimulated distally and recording is obtained from the sciatic nerve proximally (left). The latency is measured at the tip of the first peak and is divided by the distance between the stimulating and recording electrodes, giving the conduction velocity along the yellow path on the left picture. The lower tracing is the response to a single stimulus. Averaging 256 responses (upper tracing) allows the response to be extracted from the background noise (positivity downwards). (Copyright L. Poncelet)

distance between two recording points. Two recording points are not essential for SNCV measurement because the delay that occurs at the neuromuscular junction does not have to be accounted for as in MNCV measurement.

This method is demanding because the amplitude of the compound action potential in a nerve is about 10³ smaller than that in muscles. Digitization of the response and an electronic average of 200–500 repetitions are needed to extract the compound action potential from the background electronic and physiological noise (see Figure 4.10). The method is prone to contamination by reflexively triggered muscle potentials; therefore administration of a non-polarizing muscle relaxant (atracurium, 0.2 mg/kg i.v.) may be necessary. Correct placement of the stimulating and recording electrodes, and proper tuning of the stimulus intensity, is not as straightforward as in MNCV studies (Holliday *et al.*, 1977; Redding *et al.*, 1982; Van Ness, 1985).

However, considering that the fastest fibres are primarily involved in conduction velocity measurements and that the fastest sensory fibres conduct at a higher speed than the fastest motor fibres, a mixed nerve study is a reasonable substitute to evaluation of a pure sensory nerve in most instances. A mixed nerve study has the advantage of allowing electrode placement and stimulus intensity to be checked by recording the M wave in the target muscle. (see Figure 4.10). The sensory component of large stretches of mixed nerves, such as the radial or saphenous nerves, can be precisely investigated because they are associated with visible or palpable vascular structures; the accessory cephalic vein and the saphenous artery, respectively. Changes in SNCV are interpreted in the same way as MNCV changes. However, amplitude and waveform changes should be interpreted with more caution since they are highly sensitive to procedure conditions.

## H-Reflex evaluation

### Indications

Evaluation of the H-reflex allows the afferent nerve root to be tested.

## **Technique**

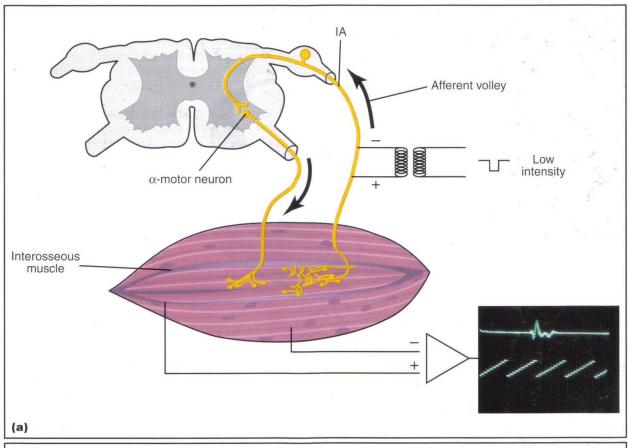
While stimulating a peripheral mixed nerve, action potentials are also elicited in sensory fibres. IA fibres forming the afferent arm of the stretch reflex (see Chapter 1) are recruited and may trigger their target  $\alpha$ -motor neurons, giving rise to the H-reflex. (H stands for Hoffman, the name of the investigator who first described such a reflex in the calf muscle of humans.) However, the antidromic volley in the motor neuron fibres cancels the reflex-elicited orthodromic action potentials by collision or by inducing a refractory period at the axon hillock level (Figure 4.11). To address this, the stimulus intensity is reduced to a low enough level to recruit IA afferents (in principle more sensitive) without recruiting motor neuron axons - in this way a pure H-reflex will be elicited. However, such a situation is observed inconsistently in normal anaesthetized dogs. With increasing stimulus intensities, F waves are superimposed and eventually largely replace the H-reflex (Poncelet and Balligand, 1991). A technique taking advantage of the double innervation of the plantar interosseous muscles (through the caudal cutaneous sural nerve and tibial nerve) may favour H-reflex recording in the hindlimb (Malik and Ho,1991).

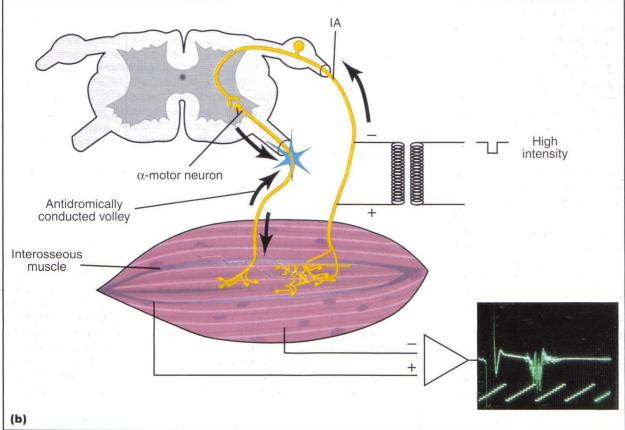
## Cranial nerves

Cranial nerve reflexes can be recorded consistently (Figure 4.12). Stimulation of a branch of the trigeminal nerve (e.g. the infraorbital nerve) and recording from a facial nerve-innervated muscle (e.g. the orbicularis oculi) can investigate the trigeminofacial reflex. If the efferent arm is first found to be normal (assessed by stimulating the auriculopalpebral branch of the facial nerve), the afferent maxillary nerve can be investigated through reflex testing. The trigemino-trigeminal reflex can be explored by recording from the rostral belly of the digastric muscle while stimulating the infraorbital nerve (Whalen, 1985).

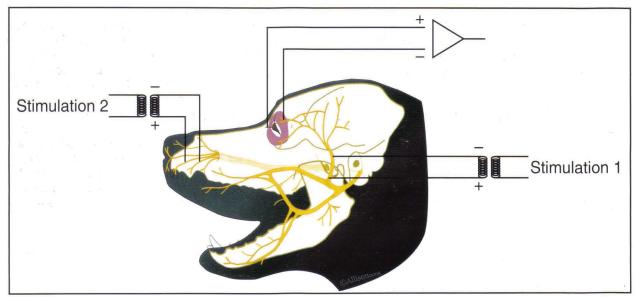
# Perineal reflex

The perineal reflex can be investigated through stimulation of the perineal skin whilst recording from the anal sphincter (Cook *et al.*, 1991).





(a) At low stimulus intensity, IA fibres, which are the largest afferents coming from the muscle spindles, may be stimulated in isolation in some dogs to give a pure H-reflex. (b) At higher stimulus intensity, antidromically conducted action potentials are elicited in the  $\alpha$ -motor neurons and cancel the reflexively triggered potentials (tibial nerve, plantar interosseous muscles; positivity downwards).



4.12 Stimulation of the infraorbital nerve (Stimulation 2) may trigger reflex responses in the orbicularis oculi muscle (V-VII reflex) innervated by the facial nerve. The efferent branch of the reflex should first be assessed by stimulating the auriculopalpebral branch of the facial nerve (Stimulation 1). (Modified from Whalen, 1985)

# **Evaluation of central afferent pathways**

# Somatosensory evoked potentials

#### Indications

Recording the electrical activity at the level of the spine or skull in response to the stimulation of a peripheral sensory or mixed nerve allows for investigation of the central (spinal cord and brain) afferent pathways and the dorsal nerve root, provided the peripheral components are intact. Such potentials form SSEPs. These techniques are not commonly performed as they usually provide little diagnostic or prognostic information. However, as techniques become more sophisticated SSEPs may play an important role in the diagnosis and treatment of spinal cord disease.

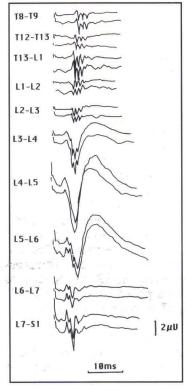
### **Technique**

The appropriate sensory or mixed nerve is stimulated as for nerve conduction studies. Stimulus frequency should be kept <4 Hz and its intensity should be monitored. The recording electrode can be seated in the interarcuate ligament at several intervertebral spaces, up to the atlanto-occipital membrane. Averaging is needed to faithfully record these low amplitude potentials as for the SNCV. Most central conduction velocity measurements are performed with two recording electrodes positioned on either side of the spinal cord region to be evaluated. The reference electrode is seated in the paraspinal muscles at least 3 cm from the midline. Evoked potentials can also be recorded from electrodes positioned over the cranium (Holliday, 1992).

Four types of potentials can be recorded over the spine:

- · The nerve root component
- The cord dorsum potential
- · The ascending evoked potential
- · The medullary component.

**Nerve root component:** The nerve root component is recorded over the L6–L7 intervertebral space (Figure 4.13). It represents the afferent volley in the dorsal roots and antidromically conducted potentials in the ventral roots. It is similar to a mixed nerve CAP.



# 4.13

Somatosensory evoked potentials recorded along the lumbar and thoracic spine in response to tibial nerve stimulation (two repetitions are superimposed). Caudo-cranially, the root component (L7-S1 and L6-L7), the large interneuronal component (from L5-L6 to L3-L4) and the ascending evoked potential (from L2-L3) can be recognized. Note that positivity is up in these tracings. (See text for details about waveforms.) (Reproduced from Poncelet et al., 1992a with permission from the American Journal of Veterinary Research)

**Cord dorsum potential:** The cord dorsum potential is essentially a near field potential best recorded over the lumbosacral spinal cord intumescence with pelvic limb nerve stimulation, or over the cervical spinal cord intumescence with thoracic limb nerve stimulation. It

contains small early deflections attributed to the intramedullary path of the afferent fibres, a large negative deflection resulting from the activity of interneurons, followed by a long duration blunted wave caused by the primary afferent depolarization phenomenon (see Figure 4.13).

Ascending evoked potential: The ascending evoked potential can be followed over the thoracolumbar and cervical spine. This is typically a CAP. Its latency increases as the recording site moves cranially. The CAP is a small amplitude potential displaying at least three successive positive/negative deflections (see Figure 4.13). Dorsal funiculi and the dorsal part of the lateral funiculi produce the majority of the potential.

**Medullary component:** The medullary component is recorded at the atlanto-occipital junction. It has the characteristics of a near field potential and is thought to result from the activation of the medullary somatosensory relay nuclei, followed by a recurrent inhibition. It is made of a negative wave followed by a blunted positive wave, corresponding to interneuron relaying and recurrent inhibition, respectively.

Scalp-recorded SSEPs display a positive/negative deflection with many characteristics of near field potentials. Later waves can be recorded but are usually cancelled by most anaesthesia protocols. Waveform and amplitude may change dramatically depending on the recording electrode position on the head. The precise neural generators have not been defined in dogs or cats.

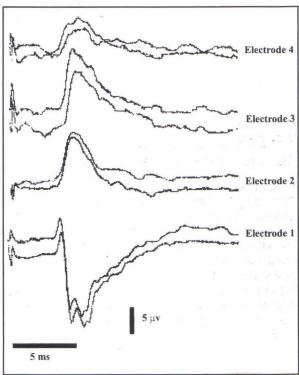
## SSEPs in spinal cord lesions

Two main goals of the neurological examination are localization of the lesion and evaluation of its severity. Several efforts have been made to use SSEPs to confirm, refine and quantify observations drawn from the neurological investigation, especially in the frequent complaint of acute, focal spinal cord damage. With increasing severity of spinal cord injury SSEPs remain recordable at the level of the scalp while undetectable at the level of the spine cranial to the lesion. However, both types of SSEP recording disappear before the subjective conscious pain perception test becomes markedly reduced or absent (Poncelet et al., 1993). Consequently, while recording SSEPs cranial to the site of spinal cord compression confirms a mild lesion, SSEP disappearance does not carry the same poor functional prognosis as does the absence of conscious pain perception (Holliday, 1992).

SSEP recording may however be of help in several situations, such as cases where imaging is unable to delineate a focal cord lesion or cases where more than one lesion is shown by imaging, and in cases of inflammatory, infectious and degenerative diseases where no macroscopic lesion is present. If more than one site of spinal cord compression is present, desynchronization of the ascending evoked potential components is evident cranial to an old clinically silent lesion (Poncelet *et al.*, 1993).

## **Evoked injury potentials**

When an ascending volley of the SSEP action potential is blocked before reaching the recording electrode, a monophasic positive potential is recorded. If it is blocked just after the recording electrode, a biphasic positive-negative potential is recorded. This transition makes it possible to precisely identify the location of conduction block along the spinal cord (Figure 4.14) Contrary to ascending evoked potentials or scalp-recorded potentials, the amplitude of the evoked injury potential (EIP) has a tendency to increase with lesion severity (Poncelet *et al.*, 1998). Unfortunately the relationship between EIP amplitude and clinical severity grading is too loose to be used as an objective measurement of lesion severity.



Evoked injury potentials (EIPs) in the vicinity of a severe disc herniation. Caudo-cranial recordings (from bottom to top) over a distance of 2 cm, demonstrating the EIP waveform change from a biphasic to a monophasic character that takes place at the conduction block location. Note that positivity is up in these tracings. (Reproduced from Poncelet *et al.*, 1998 with permission from the *American Journal of Veterinary Research*)

The EIP can also discriminate between focal and diffuse lesions. In the former, an EIP can be recorded while in the latter, progressive caudo-cranial decrement of the ascending evoked potential is expected.

## SSEP in brain lesions

With brain lesions the scalp-recorded SSEP is often abnormal. A normal medullary component excludes concurrent spinal cord or peripheral lesions. This use of SSEP has not been evaluated in veterinary medicine.

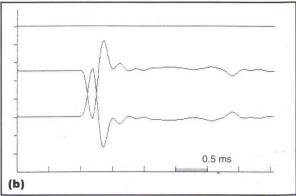
# **Special senses**

# Brainstem auditory evoked potentials

This is probably the most widely used electrophysiological test in veterinary medicine. Sounds are used to stimulate the auditory system and the resultant electrical activity is recorded from electrodes placed at strategic sites on the skull. Because auditory stimuli are used in this test the functional integrity of the structures of the outer, middle and inner ear is evaluated in addition to the nervous system.

The most widely used stimulus is the click. It is obtained by feeding a 0.1 ms rectangular electrical pulse to an ear phone – the sound stimulus reaches the ear canal via tubal inserts. The ear phone transducer reacts to this electrical stimulus by generating a short duration damped sine pressure wave. By reversing the polarity of the electrical pulse, the polarity of the pressure wave is also reversed (Figure 4.15). Most investigators work with alternating polarity click stimuli as this cancels the electromagnetic artefact from the transducer. Unfortunately, this also cancels the diagnostically relevant cochlear microphonic

(a)



(a) Set up for recording brainstem auditory evoked potentials. Recording electrodes seated at the vertex, reference electrode in the mastoid area, ground electrode in the neck area. Transducers are connected to a silicone tubing ending with a polyurethane foam cylinder fitted in the external auditory meatus. (b) A 0.1 ms rectangular electrical pulse generates a complex pressure wave that may begin with a pressure rise (condensation click, C) or a pressure drop (rarefaction click, R) according to its polarity; the upper tracing is the electronic sum of the two pressure tracings (a zero line) proving that the transducer faithfully reverses the signal.

potentials resulting from cochlear hair cell electrical activity. Each ear is tested in turn but attenuated stimuli are transmitted to the untested ear through bony conduction. To address this issue, a wide band continuous masking noise (with an intensity lower than the intensity of the click) is delivered to the untested ear.

Current information available about tone evoked auditory potentials in dogs (used to assess hearing at different frequencies) has been obtained under widely different technical conditions and cannot be effectively compared.

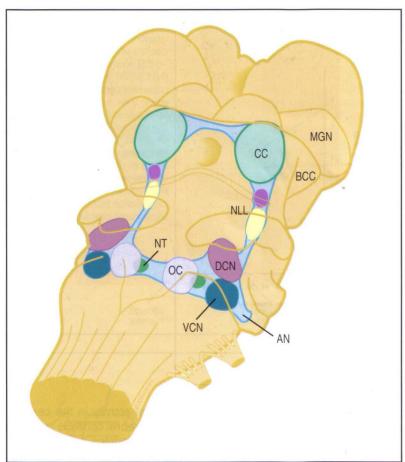
In response to click stimuli, skull electrodes record a succession of positive/negative deflections that have been divided into short, middle and long latency responses. Middle and long latency responses are extremely sensitive to arousal status and as such middle latency auditory evoked potentials have been investigated as a tool to monitor anaesthetic depth in sedated patients (Pijpendop *et al.*, 1999). The short latency responses are those evaluated when testing hearing.

Short latency responses are usually obtained in dogs and cats under sedation or anaesthesia due to poor tolerance of the skull electrodes and tubal inserts that are placed in the ears. They comprise five successive positive/negative deflections (numbered with Roman numerals). Some of the deflections, usually IV and V, may be fused and in some individuals further later deflections may be recognized. Much speculation has been made in the past about the neural generators responsible for these deflection peaks. Peak I results mostly from the afferent volley in the auditory nerve. For the subsequent deflections no simple relationship can be made between relay nuclei and peaks. It seems that all the waves, from I to V, are generated by structures caudal to the caudal colliculi (Figure 4.16). Most of the afferent fibres cross the midline and may do so at different brainstem levels.

#### **BAEP** in deafness

The BAEP recording is widely used as a screening test to identify complete deafness in individuals of breeds prone to hereditary hearing losses such as the Dalmatian (see Chapter 11). It has proven an invaluable tool in the investigation and control of congenital deafness in numerous breeds of dog. The method is objective and identifies unilateral abnormalities that subjective observation of behavioural responses to loud noise cannot do. Regardless of the methodological differences among investigators, BAEP to high intensity click stimuli (60-90 dB Normal Hearing Level) has proved very efficient (Holliday et al., 1992; Strain et al., 1992) with a very low occurrence of equivocal results in puppies. Puppies are usually tested around 45 days of age. A second test can be performed a few weeks later if the results are unclear.

Interpretation of findings: The presence of waveforms, their latency and their amplitude are all considered, although identification of congenitally deaf animals is simply based on the presence or absence of waveforms.



Schematic view of the auditory nuclei and pathways in a dog or cat brainstem. All deflection peaks (I-V) of the short latency auditory evoked potentials are generated by structures distal to the caudal colliculi (Based on Moore JK, 1987). Except for peak I, which mostly originates from the auditory nerve, no simple relationship exists between a given peak and a structure. All information eventually crosses the midline although it can do so at different levels. AN = auditory nerve; BCC = brachium of the caudal colliculus; CC = caudal colliculus; DCN = dorsal cochlear nucleus; MGN = medial geniculate nucleus: NLL = nuclei of the lateral lemniscus; NT = nucleus of the trapezoid body; OC = olivary complex; VCN = ventral cochlear nucleus.

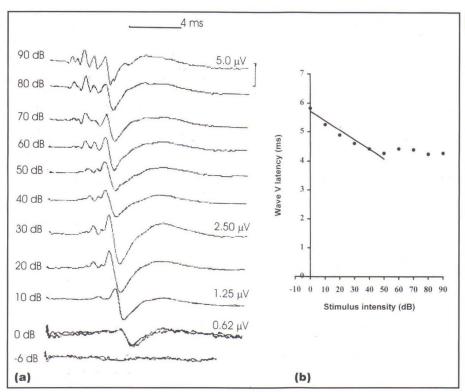
- The latency of the different peaks increases and amplitude diminishes when the stimulus intensity is lowered in normal animals. Wave V is the last wave to disappear as the stimulus intensity is reduced.
- An increase of the latency of all peaks, when using high intensity stimuli, suggests external and middle ear transmission problems since the stimulus reaching the cochlea is attenuated by pathology. The interpeak latency differences are, however, unchanged as the cochlea and brainstem are normal.
- Near normal peak I latency suggests normal cochlear and CN VIII function, while altered later peak latencies suggest brainstem involvement. Exploring the whole range of stimulus intensity may identify 'partial' hearing loss.
- The click intensity required for threshold response recording increases in the presence of transmission problems in the outer and middle ear as well as in endocochlear and retrocochlear lesions.
- Although relatively infrequently performed, partial hearing loss can be identified and investigated further by repeating the BAEP at progressively lower stimulus intensities. To do this the latency of wave V is recorded as a function of the click stimulus intensity (Figure 4.17). The slope of the curve generated from this data in the low intensity range (threshold to threshold plus 40–50

dB; defined as the regression line) is normal in conductive hearing loss (i.e. disease of the outer or middle ear) while it may be steeper in sensory hearing loss (i.e. disease of sensory apparatus of the inner ear) (Shiu *et al.*, 1997; Poncelet *et al.*, 2000). Further anatomic-functional association studies in dogs and cats are needed before these are definitive guidelines for interpretation.

#### **BAEP** in brainstem lesions

Changes in waves II–V of the BAEP have been reported in association with various brain lesions (Fisher and Obermaier, 1994; Steiss *et al.*, 1994). A common measurement made is the time elapsed from the peak of wave I to the peak of wave V. This is called the central conduction time and believed to represent the time taken for conduction through the brainstem. As expected, caudal fossa lesions can profoundly affect the BAEP but cerebral disease can also influence the recordings by causing a caudal brain shift or herniation that affects the brainstem. BAEPs are therefore not useful for precise localization of a brainstem lesion but could potentially be useful in anticipating life-threatening conditions such as intracranial pressure elevations, cerebellar herniation and brainstem compression.

BAEPs may be of special interest in vestibular syndrome where the differentiation between central and peripheral localization is of paramount prognostic significance (see Chapter 10). The intimate anatomical association between the vestibular and auditory



Short latency auditory evoked potentials in response to click stimuli of decreasing intensity from 90 to -6 dB normal hearing level (NHL) (left panel). The right panel records the latency of wave V as a function of the stimulus intensity. The slope of the regression line fitting the points in the lower intensity range may have diagnostic value in detecting partial deafness (Reproduced from Poncelet et al., 2000 with permission from the Journal of Veterinary Internal Medicine)

systems makes BAEP testing worth investigation. Frequently in peripheral vestibular disease the ipsilateral BAEP is abnormal. With central lesions, like cerebello-medullary pontine angle tumours, BAEPs to both ipsi- and contralateral stimulations may be affected since most of the contralateral afferent fibres cross the midline. In central disease, wave I may be expected to be normal as the nerve is external to the lesion, but in practice large compressive extra-axial masses can sometimes compress the peripheral nerve as it enters the brain. Such testing may improve the discrimination between central and peripheral vestibular syndrome. Confirming bilateral deafness is additional vital evidence in the diagnosis of bilateral symmetrical vestibular disease.

# Ophthalmological electrophysiological testing

Two diagnostic modalities exist to evaluate the function of the visual pathways. These are the electroretinogram (ERG) to evaluate the retina and visual evoked potentials (VEPs) to evaluate the central visual pathways. Discussion about these tests is outwith the scope of this book and the reader is referred to the BSAVA Manual of Small Animal Ophthalmology for further information (see also Chapter 9 for several specific indications of these tests).

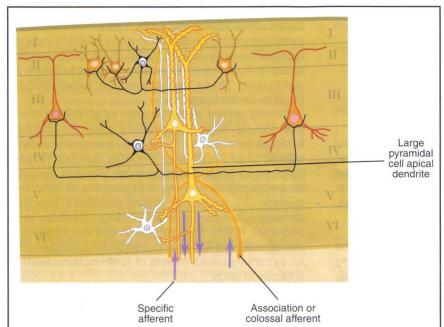
### Electroencephalography

EEG used to be a diagnostic tool for the veterinary neurologist to aid in the localization of focal lesions. The advent of advanced imaging has largely replaced EEG for this purpose but its use in investigating seizure disorders is currently expanding. EEG is the recording

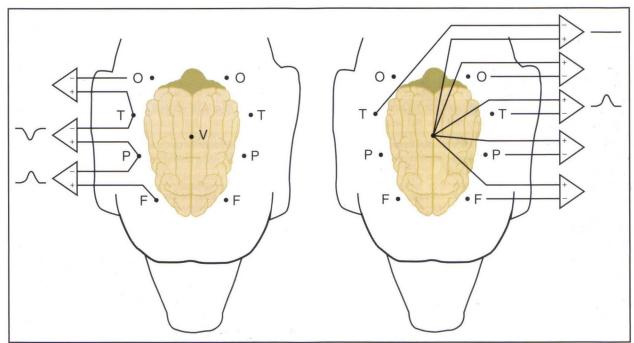
of the spontaneous electrical activity in the cerebral cortex. Organization of the cerebral cortex is relatively monotonous and the different regions are mostly distinct through their input—output relationships. The various cortical areas share a functional organization in columns perpendicular to the surface of the cerebrum. They also exhibit synchronized activity, which generates variations in potential with an amplitude large enough to be recorded from the surface of the head.

The origin of these potentials is mostly the synchronous synaptic activity along the apical dendrite of output pyramidal neurons in layers III and V, triggered by the layer IV stellate neurons that are a major input to the cortical columns (Figure 4.18). Extracellular currents are caused by synaptic activity and flow along the apical dendrites that run perpendicular to the cortex surface. Only the currents closest to the surface and running perpendicular to it influence scalp electrodes. Activity in fibres devoted to *surround inhibition*, like those of basket cells, radiates in a plane parallel to the cortex surface. This activity only contributes minimally to the surface recorded potentials. Glial cells may also generate potential changes but these are so slow that they are filtered out by most recording settings.

Needle electrodes are seated subcutaneously over the cranium. Three to four electrodes (frontal, temporal, parietal and occipital) are placed on each half of the head, as well as an additional one at the vertex level, forming the electrode 'array'. 'Montages' refer to the way pairs of electrodes are connected to the input of the amplifiers (Figure 4.19). Longitudinal montages help to identify focal electrical events that occur under the electrodes; the events are displayed with reverted polarity on two adjacent tracings. Transverse montages help to investigate the asymmetry of an electrical event.



Schematic view of the 4.18 cerebral cortex. Large pyramidal cells (yellow) in the layers III and V of the cortex send a long process towards the cortical surface; these processes receive multiple synaptic contacts from stellate cells (white) in layer IV; the stellate cells are triggered by afferents from the thalamus. The synaptic activity creates a sink near the cortex surface and a source in the depth of the cortex, near the pyramidal cell somata, resulting in currents flowing perpendicular to the skull surface and making them recordable from the scalp. Activity running in a direction parallel to the cortex surface, such as that in the basket cell processes (black), does not influence skull surface electrodes. (Modified from Martin, 1991, with permission from McGraw



Longitudinal (left) and transverse (right) common reference EEG electrode montage. In the longitudinal montage, one electrode is connected to the inverting input of one channel and to the non-inverting input of the adjacent one. A focal event (a negativity under the right parietal electrode in this example) can be detected by the reversal of its polarity in two adjacent channels. In the transverse montage all electrodes are referenced to a single vertex electrode. A focal event (a negativity under the left temporal electrode in this example) is recorded on a channel related to one half of the brain only (asymmetry detection). F = frontal; O = occipital; P = parietal; T = temporal; v = vertex.

Most investigators use sedation to record EEG as general anaesthesia can significantly affect the readings. Ideally, cortical activity during all stages of consciousness from full arousal to drowsiness, non-REM (rapid eye movement) sleep and REM sleep should be recorded. EEG tracings are prone to contamination by artefacts; eye movements, swallowing, facial and masticatory muscle activity often obscure the recordings. ECG and respiratory movements, especially panting, can also be superimposed. The examiner must recog-

nize these artefacts when visually examining the tracings and in a restless animal it can be extremely difficult to obtain a useful study.

# Interpretation

The background rhythm is a function of wakefulness:

 With full arousal the tracing displays low amplitude high frequency (15–25 Hz) activity; beta-rhythm

# Chapter 4 Electrophysiology

- With drowsiness the amplitude increases and the frequency drops (6–10 Hz); alpha-rhythm
- Non-REM sleep is also called slow-wave sleep with high amplitude low frequency (2–4 Hz) activity; delta-rhythm
- REM sleep is characterized by a return to low amplitude high frequency activity that precedes eye and extremity movements.

Normal transients, mostly spindles of sinusoidal activity, can be superimposed on to the background rhythm. Typically they are recorded bilaterally. The background rhythm depends also on the age of the patient, reaching a mature aspect from 5 months of age.

## Findings in seizure disorders

Interictal EEG spikes recorded from the head surface result from a depolarization shift in the underlying neurons giving rise to a burst of action potentials.

These findings are obtained from a subset of electrodes above an epileptic focus. This phenomenon has been thoroughly investigated in experimentally induced focal epilepsy (Ayala *et al.*, 1973). During a generalized epileptic fit, spike-wave activity is recorded from all electrodes. These oscillations are dependent on thalamo-cortical circuitry.

In one recent study Berendt *et al.* (1999) found that 65% of dogs with seizures exhibited interictal EEG abnormalities. Focal low frequency activity without spike activity was the most common finding, followed by focal epileptiform activity and generalized epileptiform activity, in decreasing order of frequency. An additional report describes interictal abnormal activity in epileptic dogs (Holliday and Williams, 1998). EEG is vital in the diagnosis and management of epilepsy in people and may become an extremely useful means of further characterizing epilepsy in dogs.

Afferent	From the periphery towards the central nervous system; also used to describe the sensory fibre.		
Amplitude	Amplitude of a potential: measured from the edge of the most positive peak to the edge of the most negative one; expressed in mV or		
Antidromic	In the reverse direction compared with orthodromic; occurs with artificial nerve stimulation.		
Complex repetitive discharges	Group of muscle fibres spontaneously firing in synchrony; typically begins and ends abruptly and holds a constant rate of firing; also sometimes called 'bizarre high frequency discharges'; can be observed in muscle or motor neuron disorders.		
Compound action potential	Sum of the contributions from the action potentials travelling in muscle or nerve fibres in the vicinity of a recording electrode.		
Dispersion	The compound action potential loses its smooth waveform and becomes dispersed when the conduction velocity spectrum of the fibre population investigated becomes discontinuous by excessive conduction slowing, causing desynchronization (due to demyelination) and/or conduction blocks.		
Duration	Compound action potential duration reflects the spread of conduction velocity range within the fibre population investigated.		
Endplate noise	Miniature endplate potentials caused by random release of acetylcholine vesicles in the synaptic cleft.		
Endplate potential	Represents single muscle fibre potential triggered by the recording needle when seated near an endplate.		
Efferent	From the central nervous system towards the periphery; also used to describe a motor fibre.		
Fibrillation potential	Spontaneous action potential occurring in a single fibre; usually bi- or triphasic positive/negative deflections.		
F wave	First recorded in the foot (F); small potentials with variable amplitude and latency observed after the direct muscle response following motor nerve stimulation; result from backfiring in some motor neurons.		
Insertional potential	Results from single muscle fibre action potentials mechanically triggered by inserting the recording needle into muscle; should stop as soon as the needle is still.		
Latency	Time from the stimulus to the onset of the first deflection (onset latency) or to the edge of the first peak (peak latency).		
Myotonic discharge	Spontaneous activity with waxing and waning amplitude and frequency recorded in muscle disorders such as myotonia.		
Nerve conduction velocity	Conduction velocity of action potentials in the fastest fibres of a nerve or nervous tract.		
Orthodromic	The direction in which action potentials progress under natural conditions; with very few exceptions action potentials always travel in same direction (from a trigger zone towards the central nervous system for sensory fibres and from the axon hillock towards the must for motor fibres) because reverse conduction is not possible due to the fibre refractory period.		
Positive sharp wave	Spontaneous action potential occurring in a single fibre; usually positive deflection followed by an extremely blunted negative one.		
Recurrent inhibition	Neurons send axon collaterals, which, by way of an interneuron, inhibit themselves or their afferents.		
Vertex	Top of the cranium; actually somewhat caudal to the bregma in dogs.		

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# Neuroradiology

# Natasha J. Olby and Donald E. Thrall

#### Introduction

The central nervous system (CNS) is encased in the bones of the skull and the spine. As a result, CNS and, to a certain extent, peripheral nervous system (PNS) disease can result both from disorders of the nervous system itself (e.g. inflammatory diseases, neoplastic and degenerative diseases) and from disorders of the bones and soft tissues that encase and protect the nervous system. Imaging of the nervous system can therefore be divided into imaging of the bones and soft tissues that surround it, and imaging of the parenchyma of the CNS and, to a lesser extent, the PNS itself. Imaging of the bones can be achieved using standard radiographic equipment but imaging of the soft tissues requires more advanced techniques such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and myelography. This chapter describes the indications for, and the advantages and disadvantages of, these imaging techniques. Particular emphasis is placed on performing and interpreting survey spinal radiographs, as this is the most accessible imaging modality for veterinary surgeons in small animal practice. It is important to understand that the results of imaging of the nervous system can only be interpreted in the context of the clinical findings of each individual animal. Many dramatic anatomical abnormalities identified using imaging can be clinically insignificant (e.g. hemivertebrae, hydrocephalus).

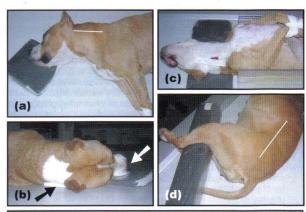
### Radiography

Radiography is commonly available to veterinary surgeons and is an extremely useful first-line imaging modality for the evaluation of bone and, to a lesser extent, the soft tissues. Spinal radiographs can be used to identify fractures and luxations, discospondylitis, vertebral neoplasia, congenital abnormalities and degenerative changes, and can provide evidence of disc herniations. In general, lesions visible on survey radiographs can be delineated more clearly using CT. Skull radiographs are not sensitive or useful in the diagnosis of intracranial disease but can be used to diagnose skull fractures, neoplasia of the skull and some meningiomas (particularly in the cat), and may be helpful in the diagnosis of otitis media and hydrocephalus.

# Spinal radiographs

# **Techniques**

Figure 5.1 demonstrates correct positioning of animals for spinal radiography.





Correct positioning to obtain spinal radiographs. The white lines indicate the level at which the beam should be centred. (a–c) The correct positioning for cervical radiography. Note that there are foam pads placed under the nose and neck of the animal (arrowed in b) to ensure that a true lateral view is obtained. (d–e) The correct positioning for thoracolumbar radiography. Note that here the foam pads have been placed between the limbs to ensure that the thoracolumbar spine is lateral.

- Radiography requires sedation or general anaesthesia in order to position the animal correctly.
- Animals should be positioned with great care, as the spine is mobile and many diseases can be worsened by movement (e.g. vertebral fracture,

- atlantoaxial subluxation). The animal may also be in extreme pain.
- In order to interpret spinal radiographs, it is important that the animal's spine is not rotated. Padding, ties and troughs should be used to achieve this end (see Figure 5.1).
- Evaluation of the width of the intervertebral disc space is an important component of the assessment of spinal radiographs. As a result of divergence of the X-ray beam, it is important to make multiple radiographs of the spine to allow accurate assessment of each space.
- Lateral and ventrodorsal views should be taken.

#### Interpretation

Accurate interpretation of spinal radiographs requires good quality images and knowledge of the normal radiographic anatomy of the spine. Figures 5.2, 5.3 and 5.4 demonstrate the salient points of normal spinal radiographs in dogs and cats. The cranial cervical spine is a particularly difficult area to interpret, especially in young animals as a result of the numerous growth plates in C1 and C2 (Figure 5.5).

Radiographs are evaluated for the following:

- Basic anatomy, including the number of vertebrae and the presence of processes and ribs (there should be 7 cervical, 13 thoracic, 7 lumbar and 3 fused sacral vertebrae in both dogs and cats)
- · Alignment of the vertebrae in two planes
- Width of the intervertebral disc space (each disc space should be compared with the disc spaces immediately cranial and caudal; only if it is not as wide as both adjacent disc spaces should it be considered to be narrowed)
- Shape and opacity of the intervertebral foramen
- Integrity of the vertebral end plates (looking for lysis and proliferation indicative of infection)
- Evidence of vertebral neoplasia in the form of lysis, sclerosis and distortion of bone outline (it should be noted that 50–75% of cancellous bone must be lost from the vertebral body before bone lysis can be detected radiographically in humans; detection of cortical bone loss is more sensitive)
- Degenerative changes of the vertebrae (e.g. spondylosis deformans) or articular processes.

# Radiographic characteristics of specific diseases

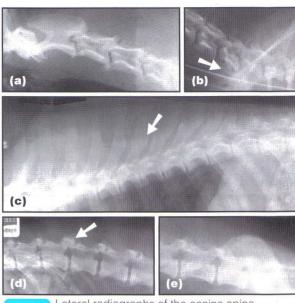
Congenital malformations: Common congenital malformations include: atlantoaxial subluxation as a result of aplasia or hypoplasia of the dens (see Chapter 14); transitional vertebrae, particularly of the lumbosacral junction (see Chapter 18); unusual numbers of vertebrae; block vertebrae; hemivertebrae and butterfly vertebrae; and spina bifida (see Chapter 15).





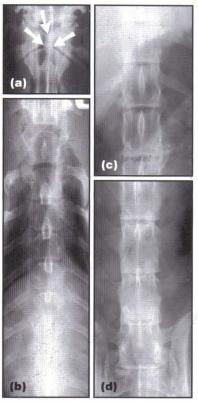
Lateral radiographs of the feline spine.

(a) Thoracolumbar spine. (b) Lumbosacral spine. Note that the lumbar vertebral bodies are long and narrow in appearance. The apparent wedging (with a broad base) of the thoracolumbar disc spaces is normal in cats.



Lateral radiographs of the canine spine.

(a) Cranial cervical spine. (b) Caudal cervical spine. Note the prominent transverse processes of the sixth cervical vertebra (arrowed). (c) Thoracic spine. Note the degenerative changes causing roughening of the border of several thoracic spinous processes (arrowed). (d) Thoracolumbar junction. There is evidence of degenerative joint disease affecting the articular processes of the first and second lumbar vertebrae (arrowed). (e) Lumbosacral junction.



5.4

Ventrodorsal radiographs of the canine spine.
(a) Cervical spine. The dens is visible on this projection (arrowed).
(b) Thoracic spine. (c) Thoracolumbar junction.
(d) Lumbosacral junction.

A lateral projection of the atlantoaxial junction in a normal 6-week-old Boston Terrier. Note the apparently separate fragment of bone (arrowed) ventral to the atlas that is part of the developing body of this vertebra.

Atlantoaxial subluxation: Lateral and ventrodorsal views are needed to evaluate the first and second cervical vertebrae. An open-mouth view has been recommended to evaluate the dens but this is not usually necessary if an adequate ventrodorsal view is made (see Figures 5.4 and 5.6). To assess the atlantoaxial articulation it is helpful to compare the alignment of the dorsal limit of the vertebral canal of C1 and C2. In animals without subluxation the alignment is essentially continuous, whereas in animals with luxation the alignment is angular (see Chapter 14). However, if the projection is not truly lateral, interpretation can be

difficult. More rarely, there can be anomalies of the occipitoatlantal junction with fusion of these two bones, associated with hypoplasia of the occipital bone, the occipital condyles and the atlas.

Transitional vertebrae: It is not unusual to find vertebrae at the thoracolumbar (TL) and lumbosacral (LS) junctions that have characteristics of vertebrae from both sections, such as an extra rib at the TL junction or lack of a transverse process at the LS junction. This is often an incidental finding but, in a study of German Shepherd Dogs with LS spondylosis, 78% of the dogs with transitional LS vertebrae had protrusion of the LS disc causing cauda equina syndrome. It was therefore hypothesized that LS transitional vertebrae decreased stability of the LS junction, predisposing to degenerative LS disease (Morgan et al., 1993). Kirberger et al. (1992) found that 11 of 36 Dachshunds that presented with intervertebral disc herniations had a congenital vertebral anomaly.

Block vertebrae: Block vertebrae result from a failure of segmentation in the developing vertebrae (Figure 5.6). They can involve fusion of the vertebral bodies, arches or entire vertebrae. They are often an incidental finding but there may be instability and an increased likelihood of intervertebral disc herniation at the site adjacent to block vertebrae (Bailey and Morgan, 1992).





5.6 Lateral and ventrodorsal views illustrating a block vertebra at C2–C3 and complete absence of the dens in a 10-year-old Poodle. The point at which the two vertebrae fuse is visible (arrowed). The dog's clinical signs related to atlantoaxial instability.

Hemivertebrae and butterfly vertebrae: Hemivertebrae result from a failure of formation of a part of the vertebra and most commonly affect vertebrae T7-T9. They are particularly common in Bulldogs and other screwtail breeds. This deformity can be an incidental finding but is more likely to be associated with clinical signs than the other vertebral anomalies. Typically, hemivertebrae are associated with deformity of the spine, usually causing kyphosis (Figure 5.7) and sometimes causing scoliosis. Neurological deficits are produced by a combination of stenosis of the canal and instability. There are reports of underlying spinal cord abnormalities, such as arachnoid cysts and syringomyelia, associated with these anomalies. MRI of the spine is therefore recommended in animals that may undergo surgery. If the central portion of the vertebra fails to develop, right and left hemivertebrae result, producing a butterfly vertebra. The name derives from a butterfly-like appearance on ventrodorsal radiographs (see Chapter 15).





Lateral radiographs of the thoracic spine in two dogs with hemivertebrae. (a) The hemivertebrae (arrowed) are not causing clinical problems. (b) The vertebral anomalies in this dog are causing severe kyphosis and paraplegia. Note the abnormal shape of the spinous processes of affected vertebrae.

Spina bifida: Spina bifida results from a failure of fusion of the neural tube and overlying tissues and is identified most easily on ventrodorsal views by the split spinous process (Figure 5.8). This may be an incidental finding but can be associated with severe neurological deficits, particularly in Manx cats with sacrocaudal dysgenesis (see Chapter 18).



5.8

Ventrodorsal radiograph of the cranial thoracic spine. Spina bifida is affecting the first thoracic vertebra. Note the duplication of the spinous process (arrowed).

**Discospondylitis:** Discospondylitis describes bacterial or fungal infection of the intervertebral disc and adjacent endplates. On radiographs it appears as lysis and sclerosis of both endplates (Figure 5.9). Multiple sites can be affected, especially in fungal infections, and so survey radiographs of the entire spine are recommended if discospondylitis is suspected (see Chapter 13).

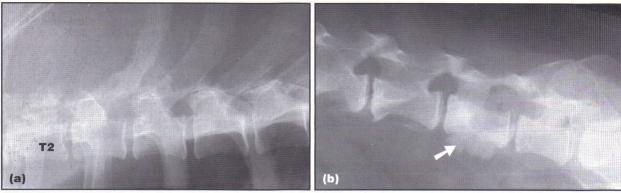




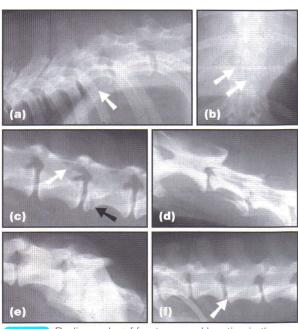
Lateral radiographs of the lumbar spine and lumbosacral junction in two dogs with discospondylitis. In both there is obvious destruction of the endplates of the affected vertebrae. (a) In addition to discospondylitis there is also sclerosis, ventral spondylosis and degenerative changes of articular processes. (b) In addition to discospondylitis there is mild ventral subluxation of the sacrum and ventral spondylosis at L6–L7 and L7–S1.

**Neoplasia:** Vertebral neoplasia is most commonly a primary sarcoma but can be metastatic. It causes bone lysis and proliferation (Figure 5.10). The intervertebral foramen and vertebral canal can be expanded by pressure from a soft tissue mass (Figure 5.10) and multiple punctate lytic lesions may be present in plasma cell tumours (Morgan *et al.*, 1980) (see Chapter 15).

Fractures and luxations: Spinal fractures and luxations occur with greatest frequency at the TL junction, the lumbar and the LS spine, and at the atlantoaxial junction, but can occur anywhere. In animals in which trauma is suspected or known to have occurred, lateral views of the entire spine should be made first. If unstable fractures are present, a horizontal beam should be used to obtain the ventrodorsal projection. If this is not possible, great care should be taken in moving the animal on to its back for ventrodorsal views. The radiographs should be evaluated for alignment, and the vertebral bodies, disc spaces and articular processes evaluated carefully (Figure 5.11) (see Chapters 14, 15 and 19).



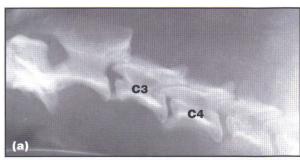
Lateral radiographs illustrating vertebral neoplasia. (a) There is almost total destruction of the spinous process of T2 by a poorly differentiated sarcoma. (b) The vertebral canal and intervertebral foramen at L6–L7 are expanded and there is new bone ventral to the body of L6 (arrowed). The cause was a poorly differentiated sarcoma.



Radiographs of fractures and luxation in the canine spine. (a) Lateral projection of the caudal thoracic spine of a dog that was hit by a car. The body of T11 appears shorter than usual and a fracture line is faintly visible (arrowed). (b) Ventrodorsal projection of the dog in (a). With this view a dramatic fracture of T11 with craniolateral displacement of the caudal fragment is evident. (c) Lateral view of the lumbar spine of a dog that had fallen from a height. Note there is a fracture of the lateral pedicle (white arrow) and of the cranial endplate of the caudal vertebra (black arrow). This was an unusual fracture that was stable. (d) Lateral view of the cervical spine of a Greyhound that had run into a tree. There is collapse of the C3-C4 intervertebral disc space and cranial displacement of the fractured caudoventral body of C3. (e and f) Common fractures and luxations of the lumbosacral articulation and cranial lumbar spine. Caudal impact combined with flexion of the spine results in fractures of the caudoventral aspect of the cranial vertebral body and malalignment in the region of the lumbosacral and thoracolumbar junctions.

**Disc disease:** Although survey radiographs are only 60–70% accurate for diagnosing the site of Hansen type 1 intervertebral disc herniations (Kirberger *et al.*, 1992; Olby *et al.*, 1994), they can provide vital information for making this diagnosis. Radiographic characteristics

of acute intervertebral disc herniations include: uniform narrowing or asymmetrical narrowing (wedging) of the disc space; mineralized disc material either within the vertebral canal or displaced dorsally within the disc space; a change in shape and opacity of the intervertebral foramen; narrowing of the articular process joint space; and, very rarely, vacuum phenomenon (Figure 5.12).

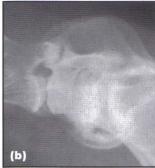


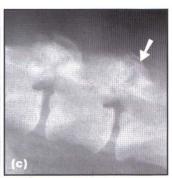


Lateral view of the spine of two dogs with acute intervertebral disc herniations. (a) Cervical spine with obvious narrowing of the C3–C4 disc space. Note that although there is no radiographic evidence of mineralized disc material on this view, CT images showed that there was a large amount of mineralized material in the vertebral canal. (b) Lumbar spine. There is mineralized disc material within the L2–L3 disc space that projects into the vertebral canal, causing opacification of the intervertebral foramen (arrowed).

**Degenerative changes:** Degenerative changes are commonly encountered in spinal radiographs of the older dog and cat, and are often clinically unimportant. They include degenerative joint disease of the articular processes, ventral spondylosis, dural ossification,







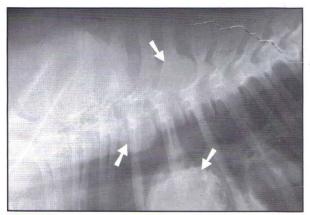
Degenerative changes commonly identified on spinal radiographs. These changes are often of no clinical significance. (a) Ventral spondylosis and sclerosis of the endplates in the thoracolumbar spine of an 8-year-old German Shepherd Dog. (b) Marked ventral spondylosis and endplate sclerosis in an 8-year-old Boxer. (c) Degenerative joint disease of the articular processes in the lumbar spine in a 4-year-old Rhodesian Ridgeback (arrowed).

and mineralization of the nucleus pulposus (see Figures 5.3 and 5.13) (Morgan and Miyabayashi, 1988; Hardie *et al.*, 2002) (see Chapter 13). Sacral osteochondrosis is an important degenerative condition reported in German Shepherd Dogs that is associated with degenerative LS disc disease (see Chapter 18).

#### Developmental disorders

Calcinosis circumscripta (Tumoral calcinosis): This is a disease in which there is mineralization of the soft tissues of the spine, usually dorsal to C1–C2 or the cranial thoracic spine (see Chapter 14).

Multiple cartilaginous exostoses: Also known as osteochondromatosis (see Chapter 15), this disorder has been reported in growing dogs. Multiple protuberances capped by cartilage develop from the cortical bone of the ribs and vertebrae. These protuberances stop growing and undergo endochondral ossification at the time of growth plate closure, but they may encroach upon the vertebral canal, causing spinal cord compression (Figure 5.14).



Cartilaginous exostoses in a 4-month-old Golden Retriever puppy. The exostoses are present on the ribs and on the bodies and spinous processes of thoracic vertebrae (arrowed).

# **Contrast techniques**

If survey spinal radiographs do not provide a diagnosis, or if they provide inadequate information for determining the optimal treatment and prognosis, the spinal cord and nerve roots of the cauda equina need to be imaged either with MRI or CT scanning, or by contrast radiographic techniques such as myelography and epidurography.

# Myelography

Myelography can be used to identify compressive or expansile lesions of the spinal cord. The benefits of myelography include: relative inexpense and availability; the ability to assess the dynamics of the spine; and the wealth of interpretative experience. The disadvantages include: the technical difficulty of the test; the side-effects (neurological deterioration and seizures); insensitivity to intraparenchymal disease; and the expertise needed to interpret a myelogram correctly.

Myelography-induced seizures have been reported to occur in 10-20% of patients and are more likely to occur in large patients (who require a larger volume of contrast medium) in which cervical injections are made (Butterworth and Gibbs, 1992; Lewis and Hosgood, 1992; Barone et al., 1998). In view of the side-effects, myelography should only be performed in animals in which signs have been localized to the spinal cord, and it is vital that the owner understands the risks and benefits before the test is performed. It is also preferable that the person who will carry out any surgery evaluates the myelogram before the study is completed, to ensure that they have all the views necessary for surgical planning. Cerebrospinal fluid (CSF) analysis, if required, should always be completed prior to performing a myelogram as the contrast medium induces mild meningitis that makes interpretation of CSF within a week of myelography difficult.

#### **Technique**

Myelography is performed by intrathecal injection of a non-ionic contrast medium (iohexol or iopamidol) via the atlanto-occipital or lumbar (L5–L6 or L4–L5) interarcuate space. Lumbar injection has the advantages of a decreased risk of iatrogenic trauma and

improved delineation of compressive lesions as the contrast medium can be forced around a site of severe compression. Disadvantages include the increased likelihood of making an epidural injection and technical difficulty of introducing a needle at that site, especially in overweight dogs with pronounced degenerative joint disease of the articular processes. It is easier to introduce the needle when performing myelography from a cervical approach but there is increased risk of iatrogenic, potentially fatal, trauma to the cervical spinal cord and/or brainstem. It is also difficult to delineate severely compressive lesions, as the contrast medium flows along the route of least resistance, which usually results in its accumulation in the ventricular system of the brain rather than coursing around the lesion.

To obtain a myelogram the animal is anaesthetized, CSF is collected for analysis and then survey spinal radiographs are obtained. The contrast medium (approximately 0.3–0.5 ml/kg bodyweight for iohexol 240) is drawn up into a sterile syringe and connected to an extension set; the extension set is filled with contrast medium (Figure 5.15). The animal is placed in lateral recumbency and the site of injection is clipped and prepared as if for surgery. A spinal needle (gauge and length depending on site) is introduced aseptically as if performing a CSF tap. The filled extension set is attached carefully to the needle once CSF appears in the needle hub and the contrast medium is injected slowly. In the case of a cervical injection, the injection is made over about 1-2 minutes and then the needle is withdrawn and images are made. In the case of a lumbar injection, the injection can either be followed with fluoroscopy or a small test injection can be made and then followed by radiography to ensure that the injection is subarachnoid prior to injecting the remaining dose.

Once the injection has been made, lateral and ventrodorsal images should be acquired as soon as possible and oblique views may be indicated. In some instances, dynamic views (traction, extension and



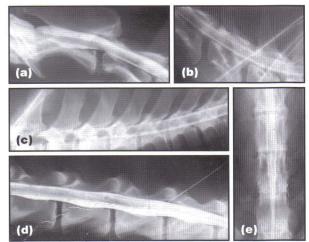
Myelography. A syringe is attached to an extension set and filled with contrast medium. The entire field should be kept sterile. The contrast medium has been passed through a 0.22 µm filter when drawn up from the bottle (see syringe with filter attachment in the foreground).

flexion) may be indicated (e.g. cervical spondylomyelopathy), but any spinal flexion and/or extension should be undertaken with extreme caution because of the potential for causing an acute concussion or compression of the spinal cord (see Chapter 14). Finally, obtaining the contralateral view often aids in identification of compressive lesions (Matteucci *et al.*, 1999).

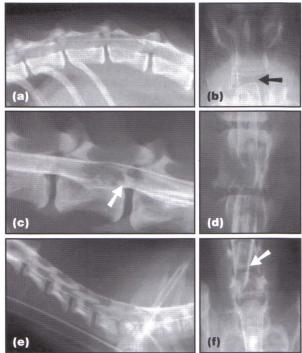
If adequate contrast medium filling is not achieved in certain areas, the animal can be tilted and bowed to allow pooling of the contrast medium by gravity. Care should be taken to keep the head elevated so that excess contrast medium does not pool in the ventricles, as this may increase the risk of seizures on recovery.

#### Interpretation

As for survey radiographs, familiarity with normal myelographic anatomy is essential. Normal myelograms are illustrated in Figure 5.16. Three basic pathological patterns are recognized in the interpretation of myelograms: intramedullary, intradural-extramedullary and extradural. Examples of each are shown in Figure 5.17. Myelographic artefacts resulting from accidental injection into the epidural or subdural (a potential space between the dura and arachnoid mater) space can complicate interpretation. Inadvertent injection into the central canal can also occur. Examples of each are illustrated in Figure 5.18. In unusual instances where there is malacia of the spinal cord, and loss of integrity of the pia mater, contrast medium may been seen within the spinal cord parenchyma (Lu et al., 2002) (Figure 5.19).



Normal myelographic appearance of the canine spinal cord with the injection being made at L5-L6. (a) The normal appearance of the cranial cervical spinal cord. (b) The normal appearance of the caudal cervical spinal cord. (c) The cranial thoracic subarachnoid space never fills well when the injection iss first made, giving the appearance of thinning or even loss of the contrast medium column. (d) The small, circular filling defect seen over the caudal aspect of L4 is most likely an air bubble accidentally introduced with the contrast medium. (e) The spinal cord tapers in the caudal lumbar spine, the level depending on the species and breed, but in general the spinal cord terminates more cranially in larger dogs. Therefore, myelography is not a useful way of delineating the contents of the vertebral canal at the LS junction in dogs.

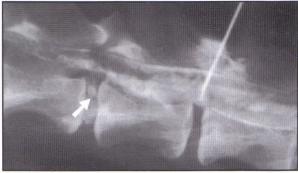


Pathological patterns recognized in the interpretation of myelograms. (a) Extradural pattern. A 1-year-old cat with lymphoma; note that the dorsal column of contrast medium is clearly deviated ventrally by an extradural mass. (b) Extradural pattern. The ventrodorsal view of the cat in (a) shows that the left lateral column of contrast medium is deviated to the right (arrowed). (c) Intradural-extramedullary pattern. Lateral view of the lumbar spine of a Labrador with a meningioma. Note that both the dorsal and ventral columns of the contrast medium column are thinned and deviate abaxially over the caudal aspect of the third lumbar vertebra as if around an intramedullary lesion. However, there is an accumulation of contrast medium in the subarachnoid space delineating an oval filling defect (the classic golf-tee sign) just dorsal to the caudal L3 endplate (arrowed). This appearance is most consistent with an intradural–extramedullary lesion. (d) Intradural–extramedullary pattern. Ventrodorsal view of the dog in (c). The deviation and splitting of the contrast medium on the right are clearly evident. (e) Intramedullary pattern. Lateral view of a 1-year-old Yorkshire Terrier that has suffered a fibrocartilagenous embolism. There is expansion of the spinal cord in the caudal cervical region causing thinning and abaxial deviation of both lateral columns of contrast medium. (f) Intramedullary pattern. Ventrodorsal view of the dog in (e). Again, note the thinning and abaxial deviation of the lateral column of the contrast medium. The endotracheal tube is arrowed. If the tube prevents accurate interpretation of the image it should be repositioned or even briefly removed to obtain a diagnostic view.





Myelographic artefacts. (a) An L5–L6 injection in which the contrast medium has entered the subdural space, causing a characteristic spindle-shaped end to the contrast medium column caudally (arrowed). (b) The contrast medium has been injected into the epidural space, causing opacification of the intervertebral foramina (short arrow) and an undulating appearance to the contrast medium column due to opacification of the venous sinuses (long arrow).



A lateral view of a myelogram in a dog with ascending myelomalacia precipitated by an intervertebral disc herniation (arrowed). There is contrast medium in the subarachnoid space and within the spinal cord parenchyma.

# **Epidurography**

Although largely replaced by CT and MRI, epidurography – the injection of contrast medium (e.g. iohexol) into the epidural space – still has a role in evaluating the cauda equina (Ramirez and Thrall, 1998). In large-breed dogs the spinal cord terminates just cranial to the LS junction and so myelography will not delineate lesions in the vertebral canal at this level. This technique is relatively simple and safe, but can result in images that are difficult to interpret because of the heterogenous filling pattern in the epidural space. Reports of the accuracy of epidurography for diagnosing cauda equina compression vary from <50% to as high as 93%.

## **Technique**

The animal is placed in lateral recumbency and a test film taken to ensure accurate lateral positioning. Following clipping and preparation, a spinal needle is introduced between the third sacral and first caudal vertebrae, or at the LS junction, and the contrast medium is injected. The volume injected depends on each case; 1–4 ml is adequate for most dogs. Radiographs should be made during the final stages of the injection as the contrast medium dissipates quickly. After making the lateral images, the patient can be carefully placed in sternal recumbency and the injection repeated to obtain a dorsoventral projection; this is helpful to lateralize compressive lesions. Following removal of the needle, extended and flexed lateral views can also be made to evaluate for dynamic lesions.

#### Interpretation

The images are evaluated for deviation of the nerve roots or filling defects and for asymmetry. The epidural space is not limited by a membrane (unlike the subarachnoid space); therefore, the outline can be indistinct and irregular. In general, if the contrast medium is deviated by >50% of the diameter of the vertebral canal, there is significant neural compression. Values of <50% are questionable. Occasionally there is filling of the vertebral venous sinuses and paravertebral veins. This is more prevalent in dogs with compressive lesions, as the increased pressure results in shunting of contrast medium into the venous system (Figure 5.20).





(a) Contrast 5.20 medium has been injected into the epidural space at the sacrocaudal junction. There is a spaceoccupying mass dorsally (arrowed) within the vertebral canal, causing ventral compression of the cauda equina. The injection has also resulted in opacification of paraspinal veins, which is more likely to occur if there is resistance to flow of contrast medium within the vertebral canal. (b) Contrast medium has been injected into the disc. Note that there is a greater than normal amount of contrast medium in the degenerative disc.

# Discography

Contrast medium can be injected directly into the L7–S1 intervertebral disc to evaluate for degenerative disc disease at this site (Ramirez and Thrall, 1998). The needle is introduced via the interarcuate ligament and contrast medium is injected into the disc. Degenerate discs are identified by the volume of contrast medium that can be injected into them (normal disc up to 0.3 ml; abnormal disc >0.3 ml), focal leakage of contrast medium into the vertebral canal at the site of disc protrusion and a heterogenous contrast medium pattern within the nucleus (see Figure 5.20). Discography in combination with epidurography is a sensitive and specific means of evaluating the LS junction (Barthez et al., 1994) but it is rarely performed now that CT and MRI are available.

# **Ultrasonography**

Ultrasound is a non-invasive and accessible imaging modality but is of limited use in the evaluation of the nervous system because the surrounding bone causes sound attenuation. However, there are specific indications for this modality (Hudson *et al.*, 1998), these include imaging of: the liver, to identify portosystemic shunts (Lamb, 1998); the brain, to identify hydrocephalus and other congenital anomalies (see Figure 5.20) (Hudson *et al.*, 1990); soft tissue masses, e.g. within the brachial plexus to aid in biopsy (Platt et al., 1999); and intraoperatively to identify and aid in the biopsy of intraparenchymal CNS lesions (Thomas *et al.*, 1993). A skilled ultrasonographer is needed to obtain and interpret the images.

The brain can be imaged most reliably via persistent fontanelles. Other windows useful in young animals with thin calvaria include the foramen magnum, the temporal fossa and the eye. The ultrasonographic anatomy of the brain has been described (Figure 5.21) and its use for identifying hydrocephalus and other congenital malformations, such as Dandy Walker syndrome, has been reported (Hudson *et al.*, 1990; Saito *et al.*, 2003; Noureddine *et al.*, 2004).



A transverse image of the brain via the bregmatic fontanelle at the level of the interthalamic adhesion. The lateral ventricles are identified by \* and the thalamus by T. (Courtesy of Dr K. Spaulding)

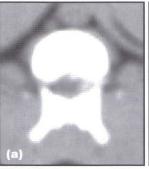
Doppler ultrasonography is also useful for evaluating blood flow in the CNS. Transcranial Doppler ultrasonography can be used to evaluate the blood flow in the basilar artery via the foramen magnum in most patients, and the cerebral arteries can be evaluated in animals with a persistent fontanelle. The resistance index, a measure of resistance to blood flow, can be calculated for the basilar artery and has been shown to be related to intracranial pressure and neurological status in dogs (Fukushima *et al.*, 2000; Saito *et al.*, 2003). The ultrasonographic and Doppler imaging characteristics of the spinal cord have also been described when imaged via a hemilaminectomy (Finn-Bodner *et al.*, 1995; Hudson *et al.*, 1995a).

# **Computed tomography**

Computed tomography, previously known as computerized axial tomography (CAT), is an imaging modality that is widely used by veterinary neurologists. Indications for its use in neurological patients include imaging of the brain and skull, the tympanic bullae, the bones of the cervical and thoracolumbar spine, the cauda equina and, in combination with myelography, the spinal cord. It can also be used to evaluate the soft tissues of the brachial plexus and to identify acute intervertebral disc herniations of mineralized disc material. It has the advantage of providing good tissue detail (particularly of bones), generating cross-sectional images that can be reconstructed in different planes and relative accessibility. Disadvantages include the need for general anaesthesia, poor spinal cord detail and limited detail of infratentorial structures. The soft tissue contrast resolution is not as good as with MRI.

# Principles and technique

CT uses the principle that the internal structure of an object can be reconstructed from multiple projections of that object. A focal anode projects X-rays through the anaesthetized animal and the dispersed and attenuated beam is collected by detectors. The anode moves in a circular direction around the object to obtain multiple projections. There are several generations of CT scanners and the most recent (third and fourth generations) have circular detectors and rapid scan times (a few seconds per slice). The information collected by the detectors represents the attenuation coefficients of the tissue through which they have passed, and sophisticated software generates images comprising a grey scale. This grey scale is made up of pixels: each pixel is the averaged attenuation of that voxel of tissue (1 voxel = 1 pixel x the slice width, which typically varies from 1 mm to 10 mm). The tissue attenuation is assigned a shade of grey compared with that of water on a scale of Hounsfield units (HU) in which water is 0, metal is +1000 (white) and air is -1000 (black). When evaluating different tissues, the range of the grey scale can be manipulated to increase or decrease tissue contrast. This is known as altering the windows. For example, when evaluating abdominal contents, a soft tissue window width of approximately 750 HU is used. For CNS, where differences in the physical density and atomic number of normal and abnormal tissue are not markedly different, a narrower window of 100-200 HU is used to increase tissue contrast resolution. A bone window is wider (e.g. 1000 HU), giving greater bone detail but decreasing soft tissue contrast. Furthermore, the level of each window can be altered to set the central shade of grey at different points in the scale. It is important to evaluate tissues in the correct window and level in order to avoid missing lesions (Figure 5.22). The digital information generated from the series of transverse images can be reconstructed to generate images in different planes (though some image detail is lost). More recent innovations enable three-dimensional reconstructions to be produced that are especially useful when viewing complex fractures.



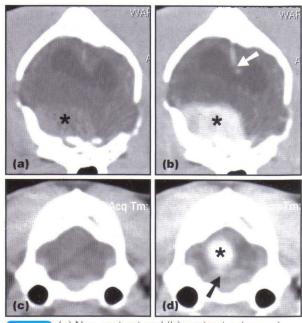


Transverse CT images of a lumbar vertebra in a Dachshund. (a) The image is being viewed in a soft tissue window (high contrast) and the presence of mineralized disc material in the vertebral canal is obvious. (b) The same image is viewed in a bone window (low contrast) and the herniated disc material is more difficult to identify.

Contrast studies are a vital part of a CT imaging protocol. Water-soluble intravenous contrast media are used at a dosage of 2 ml/kg bodyweight up to a maximum total dose of 60 ml. Ionic contrast media can be used, but non-ionic contrast media, such as iohexol 240, should be used in patients with renal disease or otherwise seriously compromised systemically. At the authors' institution, iohexol is used for all patients over the age of 7 years. In a typical study, anaesthetized patients are placed in the gantry and positioned so that they are straight (Figure 5.23). A series of noncontrast images is obtained, contrast medium is given intravenously and then another series of images is obtained immediately. Blood vessels will become hyperattentuating and visible as white structures. Any disease that causes damage to or changes in the integrity of vascular endothelium and blood-brain barrier, such as neoplasia and inflammation, will result in leakage of the contrast medium into the surrounding tissues, thus increasing the attenuation and conspicuity of lesions (Figure 5.24).



A patient positioned within the CT scanner for brain imaging.



(a) Non-contrast and (b) contrast-enhanced transverse CT brain images of a 2-year-old Boxer. The non-contrast image shows that there is clear loss of symmetry in the brain, with dorsal deviation of the right lateral ventricle and expansion of the sutures in the skull, suggesting a pressure effect. A broad-based mass can just be identified on the floor of the skull to the right of the clinoid process (\*). This mass is strongly enhanced following intravenous administration of contrast medium (\*). The blood vessels on the midline are also enhanced (arrowed), clearly showing the mass effect. The location of the mass to the periphery of the brain (i.e. extra-axial) and the strong contrast enhancement make a meningioma the most likely diagnosis and this was confirmed at necropsy. The skull sutures probably opened as a result of increased intracranial pressure in this young dog. (c) Noncontrast and (d) contrast-enhanced images from an 8year-old cat with paradoxical vestibular signs. The noncontrast image is unremarkable but in the post-contrast image there is a region of marked contrast enhancement (\*) within the cerebellum. This intra-axial lesion was caused by fungal encephalitis. Note the (normal) enhancement of the fourth ventricle (arrowed).

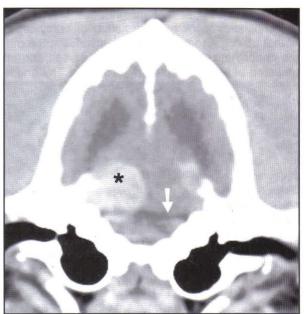
#### Interpretation

Evaluation of a CT study includes assessment for normal anatomy and symmetry (George and Smallwood, 1992), identification of areas of contrast enhancement and evaluation for artefacts. There are three main sources of artefact:

- Motion: Artefacts of motion are not problematic in veterinary neuroimaging as patients are under general anaesthesia
- Beam hardening: Absorption of lower-energy X-rays passing through regions of thick bone increases the average energy ('hardening') of the polyenergetic X-ray beam. After passing through a particularly dense bone (e.g. petrous temporal bone) from a variety of angles, the reconstruction algorithm does not allow for the unpredicted increase in energy, resulting in formation of white and black lines superimposed on the image. The caudal fossa anatomy predisposes to beam

- hardening and therefore CT is not accurate for imaging the brainstem (Figure 5.25)
- Partial volume effect: Each pixel represents an average of the tissue voxel and so the average may be unexpectedly high or low if there are adjacent fields of very different attenuation. This is usually seen where a curved object is imaged. The preceding and following slices should be evaluated to determine whether a suspected lesion is real or not, and decreasing slice thickness helps to decrease this artefact.

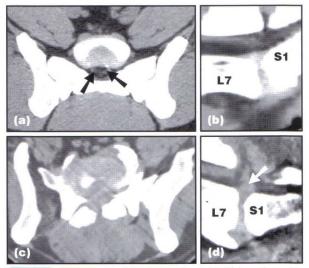
Unilateral mass lesions cause a shift in the midline of the brain (a mass effect), usually detected on contrast studies (see Figure 5.24); oedema causes hypoattenuation and recent haemorrhage is hyperattenuating. Figure 5.26 gives the range of HU for different tissues. Examples of common diseases identified on CT are shown in Figures 5.24, 5.25 and 5.27.



Transverse contrast-enhanced image of the brain at the level of the cerebellum demonstrating beam-hardening artefact (arrowed). There is also a large contrast-enhanced mass at the right cerebello-medullary pontine angle (\*\*).

Tissue	Hounsfield units (HU)	
Brain/spinal cord	25–50	
CSF - CSF	0–15	
Recent haemorrhage (<24 hours)	55–95	
Fat	-50 to -100	
Bone	600–1000	
Recently herniated mineralized disc	100-500 a	
Chronically herniated mineralized disc	450-1000 a	

5.26 Hounsfield units (HU) of different tissues. <sup>a</sup> Data from Olby *et al.* (2000).



CT images of the lumbosacral (LS) junction with a dog in dorsal recumbency. (a) Transverse, normal image. Note how the epidural fat (black on the image) surrounds the caudal equina (arrowed). (b) Sagittal, normal image of the dog in (a). Again note the epidural fat surrounding the cauda equina. (c) Transverse, abnormal image. The dog has an LS malformation with a transitional lumbar vertebra. The intervertebral disc has protruded dorsally, obliterating the vertebral canal and displacing the epidural fat, making it impossible to see the cauda equina. (d) Sagittal, abnormal image of the dog in (c). The protruding disc material is clearly evident (arrowed).

# **Magnetic resonance imaging**

The advent of MRI, previously known as nuclear magnetic resonance (NMR), has revolutionized clinical neurology, as it provides excellent soft tissue contrast resolution in multiple planes in a non-invasive manner. MRI is the imaging modality of choice for the brain, the spinal cord, the peripheral nerves and their associated plexi. The disadvantages of MRI include high cost and limited access. Care must be taken to assure the elimination of all metallic objects from the magnetic field (because of image distortion and also because the magnet transforms ferromagnetic objects into projectiles as it attracts them). The high sensitivity of the test can be problematic, in particular in the evaluation of the spine, as non-significant lesions become evident. However, this becomes less of a problem as experience in interpretation of such images increases.

#### **Principles**

Like CT, MRI provides cross-sectional images but, unlike CT, these can be obtained in any plane without detail loss (Thomson *et al.*, 1993). The images are generated by the effects of magnetic fields on protons. Most clinical magnets range from 0.5 to 3 tesla (T). MRI works by placing the object to be imaged in a magnetic field. This causes alignment of protons that are then knocked out of alignment into a different energy state by transiently applying a radiofrequency current. The subsequent decay (relaxation) of the protons as they return to their previous alignment is associated with the emission of another radiofrequency signal that is detected and used to build a three-dimensional image of

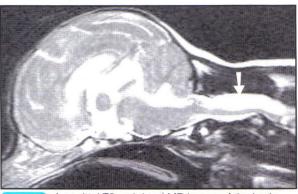
the tissue. The excitation process occurs several times to generate enough information to compose an image.

There are many different excitation/detection sequences available to accentuate different aspects of tissue. The most common pulse sequences are spinecho. The time between pulses of radiofrequency is known as repetition time (TR), and the time between the onset of a pulse applied at 90 degrees to the original magnetic field and the peak of the echo is known as the echo time (TE). The most common sequences produce images that reflect the proton density and the longitudinal (T1) and transverse (T2) forms of relaxation (Thomson et al., 1993). Contrast studies are typically performed on T1 images using intravenous gadolinium (Gd), a paramagnetic compound, chelated to diethylene-triamine-pentaacetic acid (Gd-DTPA). As for CT, damage to the blood-brain barrier results in leakage of contrast medium into the surrounding tissue, increasing the conspicuity of the lesion.

Other specialized imaging sequences are helpful for CNS imaging. It is possible to suppress the signal from fat; this is beneficial, because the high signal emitted from fat in many pulse sequences can hide smaller, adjacent lesions. In addition, pulse sequences that allow discrimination between free fluid and oedema can be used, which makes it possible to distinguish between cystic and oedematous parenchymal lesions, or to assess for periventricular oedema where the high signal from the ventricular CSF may obscure nearby oedema.

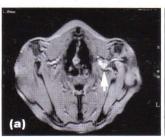
#### Interpretation

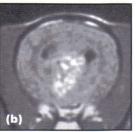
As for CT, MR images are evaluated for correct anatomy, symmetry and the presence of contrast enhancement (Kraft et al., 1989; Hudson et al., 1995b). It should be remembered that cortical bone appears black, while fat within the medullary bone can appear white. The presence of oedema is noted on proton density and T2-weighted images. There is excellent detail of the caudal fossa, and intraparenchymal lesions are visible within the spinal cord. Syringomyelia and hydromyelia, caudal fossa anomalies such as Chiari-like malformations (Figure 5.28) and brain infarcts are being



A sagittal T2-weighted MR image of the brain and cervical spinal cord in a 2-year-old Chihuahua. Cerebrospinal fluid (CSF) appears white, highlighting the ventricular system within the brain. There is a large cystic dilation in the cervical spinal cord (arrowed) and the cerebellum appears to be herniating into the foramen magnum. These findings are consistent with a Chiari-like malformation and associated syringohydromyelia (see Chapter 13).

diagnosed ante-mortem with increasing frequency now that MRI is available to veterinary surgeons. Nerve root tumours and gliomas not previously detected on CT images are also visible on MR images (Figure 5.29).





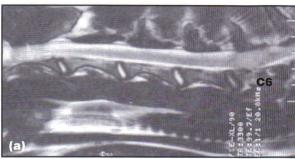
Post-gadolinium T1-weighted MR images.
(a) Brachial plexus. A nerve root tumour can be seen as a contrast-enhanced mass (arrowed). Note also the muscle atrophy of the affected limb. (b) Brain at the level of the thalamus. There is patchy contrast enhancement within the thalamus between the lateral ventricles. This intra-axial tumour was an oligodendroglioma.

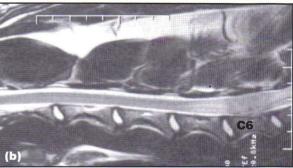
The spinal cord is usually imaged in the sagittal plane; and T2-weighted sagittal images (the so-called MR myelogram as the white CSF and epidural fat appear like intrathecal contrast medium on radiographs) are particularly useful (Figure 5.30). Transverse images of areas noted to be abnormal are obtained after the sagittal images. Degeneration of intervertebral discs is easily identified by dehydration of the nucleus, which appears grey instead of white on T2-weighted images. Interpretation of spinal MR images is difficult, due to the small size of the spinal cord in most patients and the complexity of the structures being evaluated. It is therefore important to have a spinal MR image interpreted by an experienced radiologist and to ensure that the findings are complementary to the clinical findings.

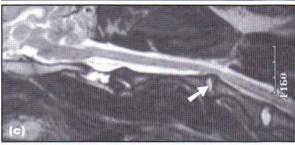
# **Scintigraphy**

Scintigraphy is only available at specialist (usually academic) institutions because of the need for specialized cameras and the use of radioactive material (Daniel et al., 1992). Conventional scintigraphy of the nervous system or other parts of the body produces planar images that identify areas where the bloodbrain barrier has broken down and fails to exclude the injected radionuclide. The drugs most commonly used are technetium-99m-diethylene-triamine-pentaacetic acid (99mTc-DTPA) and 99mTc-glucoheptonate (99mTc-GHA). As this technique gives little spatial resolution, it has been supplanted by CT and MRI. Indications still pertinent to veterinary neurology include the use of rectal scintigraphy to diagnose portosystemic shunts (Daniel et al., 1991) and conventional scintigraphy to screen animals with non-localizable pain or multifocal diseases such as multiple myeloma.

Improved detection systems and radiopharmaceuticals have improved the capabilities of scintigraphy and led to the evolution of single photon emission scintigraphy (SPECT) and positron emission scintigraphy (PET). Improved detection systems have







(a, b) T2-weighted sagittal MR images of the cervical spinal cord of a 10-year-old Labrador Retriever with a meningioma at C6. The subarachnoid space is markedly attenuated in the region of the tumour and the diameter of the spinal cord is increased. Note the intra-axial oedema adjacent to the mass. (c) T2-weighted sagittal MR image of a 2-year-old Rottweiler with a protruding intervertebral disc at C2–C3. The disc is dehydrated and therefore less bright (arrowed) and there is mild compression of the overlying spinal cord. This was also evident on transverse images.

allowed tomographic images to be obtained, analogous to cross-sectional CT images. In SPECT scanning, cerebral blood flow can be evaluated following administration of radionuclides that can cross the blood-brain barrier, such as 99mTc-HMPAO and <sup>123</sup>I-IMP. These labelled drugs diffuse across the blood-brain barrier but are then retained in the brain at a fixed site for the duration of the study by conversion from lipophilic to lipophobic forms. This technique has been used widely to assess regional blood flow in humans and its use has also been reported in dogs (Peremans et al., 2001). In PET scanning, the metabolic properties of the brain are evaluated using a positron-emitting radioisotope. The most commonly used isotope is 18F-2-deoxy-2-fluor-D-glucose (18FDG). This chemical is transported like glucose and is metabolized by hexokinase, in the same manner as glucose, to <sup>18</sup>FDG-6-P, a product that cannot undergo glyolytic metabolism and is not transportable across membranes. It is therefore

trapped at the site of initial metabolism. Measurement of uptake of 18FDG represents the rate of glucose metabolism. The need for specialist imaging equipment to complete PET and SPECT scanning puts them out of reach of most veterinary institutes, but as these techniques are developed it is possible that they will become a part of the evaluation of the neurological veterinary patient.

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# **Tissue biopsy**

# Sam N. Long and T. James Anderson

# Introduction

Obtaining tissue to establish a pathological diagnosis is a valuable tool in the investigation of disease. However, it should be remembered that the first duty of the clinician is to minimize harm to the patient in the process of obtaining a diagnosis. This applies particularly when performing a biopsy on the central nervous and neuromuscular systems, as even minimal damage to these tissues can cause significant and irreversible loss of function. It is therefore important that the clinician understands which parts of the nervous and neuromuscular systems can be sampled safely.

A biopsy may not provide a definitive diagnosis but rather may indicate the nature of the pathological process involved. Although identification of the process may not specify an aetiology, understanding the nature of the disease can help with therapy and prognosis. In this situation it is important that any changes observed by the pathologist are interpreted in conjunction with other information about the patient to refine the diagnosis. Therefore, the better informed the pathologist is by the veterinary surgeon, the more specific the investigation of the tissue can be.

This is particularly important if the sample has been derived by either fine needle aspiration or stereotactic needle biopsy (see Brain biopsy) as the number of cells obtained is likely to be smaller than with conventional biopsy. It should be remembered, however, that even conventional biopsy will sample only a proportion of the entire lesion and may not represent the entire pathological process. Thus, if biopsy findings are not compatible with the patient's clinical picture and other information (such as history, likely differential diagnoses and response to treatment), an attempt should be made to determine whether the tissue sampled is from a representative area of the lesion.

# Sample submission

Careful planning is necessary and it is essential that the clinician communicates ahead of time with the pathologist who will examine the sample. This is important firstly to ensure that the biopsy targets the most appropriate area of the tissue involved, and secondly because of specific issues that apply to processing and transporting biopsies of muscles, nerves and brain.

- Comprehensive evaluation of muscle fibres requires snap-frozen tissue (typically in isopentane, super-cooled in liquid nitrogen), and access to suitable facilities is limited.

  Consequently, if snap-freezing is not possible, some laboratories may recommend standard fixation in 10% buffered neutral formalin (BNF) whilst others may accept samples sent chilled without fixation, for subsequent freezing.
- Nerve samples require fixation in both 10% BNF and 2.5% glutaraldehyde for full examination (see Nerve biopsy).

It is therefore important that the clinician seeks advice from relevant specialists in this field to identify suitable laboratories, and plan the biopsy procedure carefully. It is also important that the veterinary surgeon understands the preferences and requirements of the laboratory that will process the samples.

Samples sent cooled on dry ice and in fixatives are considered hazardous and legal requirements for packaging and labelling must be fulfilled. Additionally, it may be desirable to send samples internationally for expert examination and in this situation customs requirements must also be met. For these reasons the clinician must arrange a suitable carrier, who has experience in transporting potentially hazardous biological specimens, beforehand. The time delay between taking the sample and its arrival at the laboratory must also be considered when being sent internationally to avoid the sample arriving at its destination outside normal working hours and therefore being likely to deteriorate.

# **Muscle biopsy**

# Indications

The decision to proceed to biopsy is clear where muscle involvement is easy to identify. Clinical signs of muscle disease include:

- Muscle hypertrophy
- Muscle atrophy
- Contractures.

Other indications for muscle biopsy include:

 Weakness, stiffness or pain localizing to the neuromuscular system  Results of diagnostic tests that support muscle disease (e.g. electromyography (EMG), persistently elevated serum creatine kinase (CK) concentration, myoglobinuria)

#### Tissue selection

The selection of tissue for biopsy depends on whether the underlying problem is:

- Generalized
- · Local to a specific muscle
- Restricted to a particular muscle group (e.g. temporalis muscles in masticatory muscle myositis).

In generalized disease, muscles should be selected for biopsy so that the diagnostic yield is maximized but morbidity is minimized; most laboratories prefer biopsy samples from two different muscles. Histological and histochemical characteristics vary between individual muscles reflecting their physiology; ideally the selected muscle should be well characterized to aid interpretation.

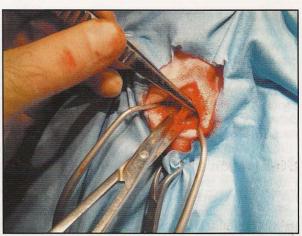
Standard biopsy sites from the pelvic limb include proximal muscles such as the vastus lateralis or biceps femoris, and from the thoracic limb include the triceps muscle. If neuropathy is likely, biopsy of the distal limb muscles, such as the cranial tibial muscle from the pelvic limb and the extensor carpii radialis from the thoracic limbs, is suggested. Alternatively, the selection of biopsy site may be guided by EMG examination. If nerve pathology is also suspected, a combined nerve and muscle biopsy should be considered; this may determine which muscle to biopsy if both are to be undertaken through one incision.

Severely fibrotic (endstage) tissue should be avoided as it is unlikely to be informative as to the nature of the process or aetiology of the disease. Areas that have been subject to invasive investigations, such as the insertion of EMG needles or previous biopsies should also be avoided (EMG studies should be planned with potential for biopsy in mind). Specimens should be harvested away from tendinous insertions as the normal histology of these areas can be confusing.

#### **Techniques**

# Open biopsy

An open approach is the standard method for muscle biopsy as it provides good and safe access, leading to confident identification of the sample tissue (Figure 6.1). This approach also allows an adequate tissue volume to be collected. The use of special clamps has been advocated to maintain the orientation and prevent contraction of muscle; however, the use of such clamps demands a relatively large biopsy site and diagnostic samples can be obtained without their use. The disadvantages of the open approach are the need for general anaesthesia and the relatively invasive nature of the technique, which mitigates against sampling multiple sites.



Open muscle biopsy procedure. Self-retaining retractors are of great value in maintaining exposure during this procedure.

Once the skin and overlying fascia have been incised to expose the muscle, the orientation of the fibres should be established. Parallel incisions are made in the direction of the fibres (Figure 6.1). A specimen should be about 0.25–0.5 cm in width and depth, and 1–2 cm in length. The ends are transected and the sample lifted clear, with care being taken to manipulate it by the ends only and thus minimize crush artefact. The defect and overlying tissues are closed routinely.

#### Needle biopsy

Needle biopsy has been described in the dog for research purposes but has not become adopted as routine practice. Although there are advantages of low morbidity and the possibility of performing the technique under sedation, disadvantages include the requirement for specialized equipment, potential problems with confidence in the tissue sampled, difficulties with sample orientation, and potentially poor tissue yields.

## Complications

Complications following muscle biopsy are rare; if performed correctly, this is a minor procedure. Haemorrhage, swelling and haematoma formation are potential complications but are uncommon. Such events are usually related to patient interference with the surgery site and are managed in a routine fashion. Although open muscle biopsy may result in an appreciable defect at a single site in a large muscle, this is not a significant problem for the majority of patients. An appropriate biopsy is unlikely to result in long-term degradation of muscle function.

# Tissue handling and processing

A complete histopathological examination of muscle involves many techniques that cannot be performed on traditional formalin-fixed material alone and requires fresh-frozen tissue. The sample is usually placed in a saline-moistened gauze and shipped overnight under refrigeration. Freezing is only undertaken if liquid nitrogen and isopentane are available.

# Chapter 6 Tissue biopsy

Specimens fixed in formalin (10% buffered formal saline) are not without value, although they cannot be characterized as extensively as frozen tissue. Samples for examination by electron microscopy are collected into special fixatives containing 2.5% glutaraldehyde. Samples that are immersion-fixed should be attached to a splint, such as a tongue depressor, using a 25-gauge needle, to prevent contraction during fixation and reduce artefact.

# **Examination and interpretation**

Frozen tissue is required to take advantage of the full range of enzymatic and immunohistochemical techniques that have been developed for the characterization of muscle biopsy specimens. General morphological examination can be undertaken on both frozen and fixed tissues. The major features of morphological interest are:

- Muscle fibre type and distribution
- · Muscle fibre shape and size
- Presence of degeneration/regeneration ± necrosis
- Distribution of nuclei
- · Presence of vacuoles or inclusions
- Cellular infiltrates.

#### Muscle fibre type and distribution

Myofibre typing is achieved by histochemical techniques that identify the presence of enzymes or substrate in the tissue. This technique is based on the myofibrillar adenosine triphosphatase (ATPase) reaction under different pH conditions, which identifies two major muscle fibre types and a number of subtypes (Figure 6.2). Most normal muscle fascicles contain a mixture of fibre types and hence there is a mosaic appearance with ATPase staining (Figure 6.3).



Mosaic appearance of normal muscle stained with ATPase (pH 9.8). The darker fibres are the 'fast' type II myofibrils. Original magnification X80.

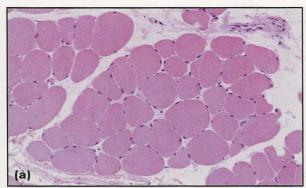
The proportions and distribution of myofibre types may be altered by disease and any changes must be put in context of the particular muscle sampled. There may be a general change in the proportion of myofibre types (e.g. type I fibre predominance in Labrador Retriever myopathy) or loss of the mosaic pattern, producing large groups of single fibre types (fibre type grouping) as a result of reinnervation. Determining whether there is selective increase or loss of a particular myofibre type requires quantitative analysis, which is time-consuming.

#### Muscle fibre shape and size

Healthy muscle fibres have a polygonal shape and smooth outline (Figure 6.4). Myofibre diameter is variable and reflects the specific muscle sampled, the region within the specific muscle, patient age and size. Changes in the shape and cross-sectional area of myofibres within fascicles suggest disease. The major patterns and their significance are described in Figure 6.5.

Muscle type	ATPase immunostaining	Physiological properties	Comments
	pH 4.3 (reversal) dark pH 4.6 dark pH 9.8 light	Predominantly aerobic with oxidative metabolism (slow contraction/fatigue-resistant/postural muscles)	
II: IIA	pH 4.3 (reversal) light pH 4.6 light pH 9.8 dark	Predominantly anaerobic with glycolytic metabolism (fast contraction/phasic movement/ movement muscles)	en sages
IIB	pH 4.3 (reversal) light pH 4.6 intermediate pH 9.8 dark	A Things of Charles we will be a compared to the compared to t	Not present in dogs
IIC	pH 4.3 (reversal) intermediate pH4.6 intermediate pH 9.8 dark	製造的に対象の対象 (Tit added) 一年のの対象をある。 (Addedを発生 patential action	Rare except in neonates or may be seen with myofibre regeneration
IIM	pH 4.3 intermediate pH 4.6 dark pH 9.8 dark	Specialized type II fibres that are primarily muscles of mastication	Specific to the dorsal muscles of first branchial arch origin

Classification of muscle fibre types. Optimum pH varies with species.





A normal muscle in transverse section is composed of groups of myofibrils with similar diameters, a smooth polygonal outline and peripherally located nuclei. Atrophy of specific myofibrils produces a characteristic angular cross-sectional outline.

(a) Normal muscle. H&E stain; original magnification X60.

(b) Myopathy in a cat. Note the atrophied fibres scattered through the muscle. H&E stain, original magnification X25.

Finding	Process	
Atrophy: Angular Small group Large group	Neuropathy but can be observed as a non-specific finding with myopathy	
Necrosis	Myopathy	
Infiltrate	Myopathy	
Myofibril regeneration	Myopathy or neuropathy	
Cellular infiltrates Accumulation of substrates (e.g. glycogen) or cellular organelles (e.g. mitochondria)	Myopathy	

Pathological findings observed in myopathicand neuropathic muscle disease.

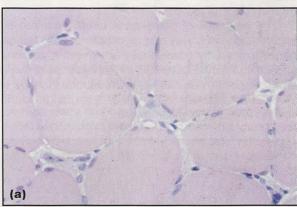
Angular atrophy of type I and type II muscle fibre types is a hallmark of denervation. Atrophic fibres have a reduced cross-sectional area and sharp, pointed projections (see Figure 6.4). In early denervation, single atrophic fibres are scattered through an affected muscle.

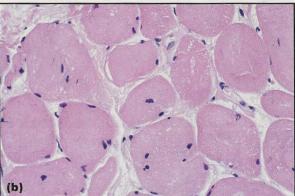
As denervation progresses, small and large groups of atrophic fibres develop. Occasionally unaffected myofibres may develop compensatory hypertrophy resulting in an excessive variation in muscle fibre size. If atrophy of all myofibres occurs at a similar time a round or polygonal shape is observed.

Myofibres may undergo splitting as a non-specific event, usually associated with myopathic disease, although this can be a normal finding at the musculotendinous junction. Depending on the plane of section the nuclei may appear internalized (see below).

#### Degeneration/regeneration ± necrosis

Regenerating muscle fibres are smaller in diameter than normal fibres, with a basophilic appearance in sections stained with haematoxylin and eosin (H&E) (Figure 6.6a). These immature fibres have increased numbers of normally situated nuclei. In contrast, necrotic muscle fibres show a decreased intensity of staining with enzymatic and traditional histochemical techniques, giving rise to 'ghost fibres'. They tend to have an increased density of central nuclei (Figure 6.6b) and there may be a monocytic infiltrate. It should be noted that degeneration of muscle fibres does not necessarily lead to necrosis. Endstage degenerate muscle fibres are replaced with connective and adipose tissue in varying proportions.





(a) Regenerating myofibrils are reduced in diameter and have a basophilic appearance on H&E staining. Original magnification X100. (b) In some myopathies there is central migration of the nuclei. H&E stain; original magnification X100.

# Distribution of nuclei

Muscle fibre nuclei are normally distributed peripherally around the sarcolemma. A central location may be observed in both myopathies and neuropathies and is not a finding specific to either (see Figure 6.6b). In general, if more than 1% of the nuclei are central, this is interpreted as abnormal.

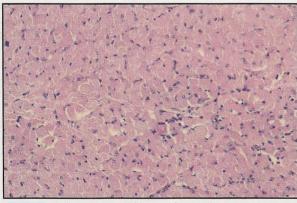
#### Presence of vacuoles and inclusions

Abnormal deposits of substances, structures and organelles may be observed microscopically or ultrastructurally. Accumulations may represent excess substrate, product or abnormal cellular components depending on the underlying disorder. Metabolic disorders will result in accumulations of substrate or product, depending on the point at which the pathways are disrupted, within the muscle fibres. These accumulations may be seen as vacuoles of material (e.g. glycogen or lipid) (see Chapter 17) or accumulations of cytoskeletal elements (e.g. mitochondria in 'core-like' myopathy of the Great Dane) (see Chapter 17).

#### Cellular infiltrates

Accumulations of lymphocytes, neutrophils, eosinophils and macrophages may occur in myositis. These may cluster around blood vessels or abnormal tissue components within either muscle or nerve fibres. Occasionally neoplastic lymphocytes may be present with multicentric lymphoma. Primary muscle tumours are occasionally observed but muscle is not a common site for metastatic disease.

The presence of parasites is usually marked by inflammatory infiltrates and myofibre necrosis but organisms are only occasionally observed in sections stained routinely (Figure 6.7). Immunostains are available for specific parasites (e.g. *Neospora*; Lindsay *et al.*, 1999). Parasitic and protozoal cysts can be found with no evidence of inflammation.



6.7 Inflammatory infiltrate of muscle due to neosporosis. H&E stain; original magnification X25.

#### Staining

For a list of histological and enzymatic stains and their applications see Figure 6.8.

The use of immunostains is of value in specific circumstances (e.g. confirmation of Duchenne's type muscular dystrophy by demonstration of loss of dystrophin). Panels of immunostains may be of value in describing unusual myopathies by further characterizing the nature of the abnormality.

# Summary of interpretation

In most cases evaluation of a muscle biopsy should confirm or deny the presence of a myopathy or neuropathy (see Figure 6.8). The value of having biopsy

Stain/enzyme	Applications	
Haematoxylin and eosin (H&E)	General stain for morphological assessment of cells and nuclei of all tissue Necrotic fibres have reduced stain uptake Degenerating/regenerating fibres are basophilic	
Modified Gomori trichrome	General stain for morphological assessment of cells and nuclei of all tissues Useful for demonstrating nemaline rods	
Myofibre adenosine triphosphatase (ATPase)	Identifies functional fibre type (see Figure 6.2)	
Periodic acid–Schiff (PAS)	Glycogen storage disorders	
Acid phosphatase	Lysosomes in myofibrils and macrophages	
Oil Red O	Triglyceride fats Identification of lipid storage disorders	
Alkaline phosphatase	Possibly useful in identifying regenerating fibre and proliferating connective tissues	
Nicotinamide adenine dinucleotide– tetrazolium reductase (NAD-TR)	Identifies mitochondrial oxidative enzyme Stains mitochondria and sacroplasmic reticulun Highlights mitochondrial-rich fatigue-resistant fibres and angular atrophied fibres Useful for identifying mitochondrial aggregates tubular aggregates and pyknotic nuclear clump	
Succinate dehydrogenase (SDH)	Identifies mitochondrial oxidative enzyme Specific to mitochondria	
Cytochrome-c oxidase (CcO)	Identifies mitochondrial oxidative enzyme Specific to mitochondria	
Staphylococcal protein A-horseradish peroxidase	n immunoglobulin seradish May detect antibodies at the neuromuscular	
Esterase	Identifies neuromuscular junctions Also stains lysosomes of myofibrils and macrophages	

The application of histological and enzymatic staining to muscle samples.

material from a representative nerve and associated muscle is self-evident. Non-specific myofibre atrophy is occasionally found since atrophy may be a result of many insults including disuse and cachexia, and interpreting this finding is dependent upon good clinical detail and thorough investigation.

Establishing whether a process is inflammatory represents a significant step in assessing the nature of the disease and may indicate a specific diagnosis or a rationale for therapy, even if the specific aetiology remains uncertain. The major decision to be made is whether evidence of inflammation suggests an infectious or immune-mediated aetiology. Being able to put the findings in context of the clinical scenario is important for the pathologist in advising the veterinary surgeon, and perhaps, suggesting further avenues of investigation.

# **Peripheral nerve biopsy**

#### Indications

Clinical evidence of peripheral nerve disease (see Chapters 2 and 14) supported by electrophysiological evidence of nerve dysfunction (see Chapter 4) are prerequisites for electing to perform a nerve biopsy.

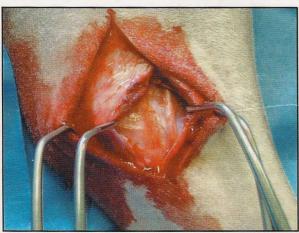
#### Tissue selection

Theoretically, a biopsy can be performed on any nerve. However, the practicalities of surgical access and potential for dysfunction following biopsy are major considerations. For example, a biopsy is rarely undertaken on the cranial nerves because of their surgical inaccessibility, and the likelihood and consequences of subsequent dysfunction.

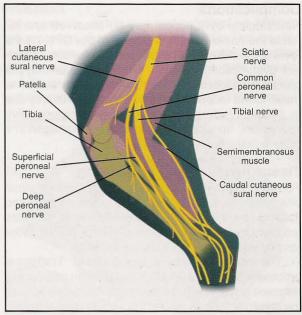
The tissue for biopsy may be indicated by localized dysfunction. Alternatively, for more generalized conditions the nerve selected should be based upon the following factors:

- · Ease of surgical access
- Likely subsequent dysfunction
- Specific clinical deficit (motor versus sensory)
- The normal characteristics of the nerve under consideration as a basis for interpretation
- The normal characteristics of associated muscle if a combined nerve/muscle biopsy is planned.

The common peroneal nerve (CPN) is an example of a peripheral nerve with established morphological and electrophysiological data associated with a well characterized muscle (i.e. cranial tibial muscle). The CPN has the advantage of being easily accessed and identified (Figure 6.9). However, as with the majority of peripheral nerves, the CPN is a mixed nerve, i.e. containing both motor and sensory fibres. The availability of predominantly sensory nerves is limited; the caudal cutaneous antebrachial nerve (thoracic limb) and caudal cutaneous sural nerve (pelvic limb) (Figure 6.10) are examples.



Common peroneal nerve biopsy. The use of self-retaining retractors is of great value. The nerve lies beneath the fascia of the biceps femoris muscle, which is incised to reveal the nerve. The nerve is divided longitudinally using fine sutures to support the extremities and reduce artefact.



6.10 Schematic lateral view of the pelvic limb, demonstrating peripheral nerve locations when considering biopsy.

Biopsy of nervous structures where there is a high likelihood of subsequent dysfunction (e.g. cranial nerves) is usually avoided, although it may be necessary on occasion during cytoreductive procedures. Biopsy of proximal peripheral nervous tissue and nerve roots, as indicated by electrophysiological studies, is possible but requires significant surgical dissection and experience in identifying the relevant tissue for sampling. If a nerve root biopsy is performed, ideally a dorsal root should be selected to minimize motor dysfunction, although single ventral nerve roots can be removed causing little or no dysfunction.

Nerve tissue may also be found within muscle biopsy material and is of potential value in assessing the distal nerve branches as well as secondary consequences on muscle morphology.

#### **Techniques**

Peripheral nerves must be visualized by an open approach. The majority of nerves are biopsied by transecting approximately a third of the width of the nerve and removing fascicles about 1 cm in length, taking care not to transect the entire width of the nerve. Care in handling the specimen is important and the sample should only be handled at the ends to preserve a region free of potential artefact; this may be achieved by placing fine sutures in each extremity. Terminal branches of sensory nerves may be removed entirely. Prerequisites of this procedure are:

- · Competent soft tissue handling skills
- · Good condition of instruments.

Complete descriptions of this procedure have been published elsewhere (Dickinson and LeCouteur, 2002).

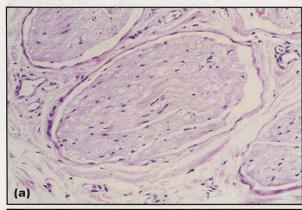
# Complications

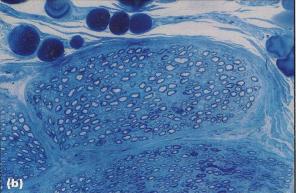
Neurological dysfunction may be observed and reflects the nerve sampled. Biopsy of the CPN (at the level of the stifle) rarely produces deleterious persistent dysfunction, although the biopsy site may be painful postoperatively. Wound problems similar to those found following a muscle biopsy, primarily due to patient interference and excessive postoperative movement, may be observed and are managed in a routine fashion.

# Tissue handling and processing

Portions of nerve should be fixed with a longitudinal orientation (e.g. by pinning to a piece of cork and floating tissue immersed in the fixative) to minimize artefact; however, samples should not be placed under tension as this may itself create artefacts.

The choice of fixative is significant. Traditional processing utilizing 10% BNF and paraffin embedding removes lipids, which represent approximately 50% of the myelin sheath, impairing the visualization of myelin sheath structure. An alternative fixative and embedding technique, using glutaraldehyde and resin, is required for the best preservation of anatomical detail (Figure 6.11). Paraffin-embedded sections are of value, however, in assessing infiltrates and may give some information on myelin structure.





Transverse sections of a normal peripheral nerve showing the effects of fixation techniques on the appearance of the myelin sheath. (a) BNF fixation, paraffin embedding and H&E staining. Original magnification X100. (b) 2.5% glutaraldehyde fixation, resin embedding and azure blue staining. Note the distinct appearance of the myelin sheath in the resin-embedded section. Original magnification X100.

Frozen sections are not prepared routinely. Frozen sections may be required for special techniques (e.g. immunolabelling/enzymatic techniques) and might be recommended by the pathology laboratory depending on circumstances (see above). Teased nerve fibre preparations are rarely undertaken but may be useful in assessing demyelination or the distribution of pathology along axons. However, this is a specialized technique that is only undertaken in laboratories that routinely process peripheral nerve samples.

# **Examination and interpretation**

Paraffin-embedded samples are examined using routine stains for tissue structure and cellular components. Routine histopathological examination might establish axon density and myelin status. Resin embedding is more appropriate for examining myelin structure, at both the light microscope and ultrastructural (electron microscopy) levels. Teased preparations are of value in ascertaining the distribution of pathology along an individual axon. Electron microscopy (EM) is of value in examining unmyelinated fibres in addition to cellular and myelin sheath ultrastructure (e.g. mitochondria). Neither electron microscopy nor teased preparations are undertaken routinely.

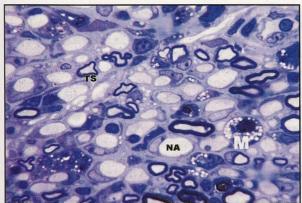
The major features of interest when evaluating a peripheral nerve are:

- Axon structure and density
- Myelin sheath thickness and integrity
- Schwann cell population (health and numbers)
- Support tissues (blood vessels and fibrous sheaths)
- Evidence of an infiltrate (distribution and nature of cells)
- Neuronal cell population (only relevant to dorsal root ganglion biopsy).

#### **Axonal changes**

Axonal changes observed range from evidence of dystrophy through degeneration to complete loss. These changes may affect axons of either large or small diameter, or may be generalized, and this may be relevant to the underlying aetiology. Loss of axons may be secondary to traumatic, toxic and metabolic insults in addition to loss of motor neurons or axonopathies of undetermined cause. When an axon is transected, the distal axon undergoes a stereotyped sequence of degenerative cellular events with disappearance of the axon and myelin. This process is called Wallerian degeneration.

Axonal dystrophy may be seen as axonal swelling, referred to as spheroid formation, with secondary loss of myelin in the area of the swellings. Spheroids contain accumulated cell components, the nature of which can be confirmed by ultrastructural examination. Axonal dysfunction may also be accompanied by the formation of large myelin ovoids and myelin balls, with evidence of remyelination if the axon survives. Lipid may be noted accumulating in local macrophages (Figure 6.12).



6.12 Demyelinating peripheral neuropathy in a dog. Myelin loss (naked axons, NA) and possible remyelination (thin myelin sheaths, TS) are evident. Note the macrophage with foamy cytoplasm (M); these inclusions contain lipid from the breakdown of myelin. Resin-embedding and azure blue, original magnification approx. X250. (Courtesy of Professor Ian Griffiths, University of Glasgow)

# Myelin changes

Care must be taken when interpreting myelin changes because artefacts are common if the tissue is handled, fixed or processed suboptimally. Myelin changes may affect specific populations (sizes) of axons or may be a general event. Primary demyelination leaves the axons intact. The myelin sheath may be thinner or thicker than normal, show evidence of degeneration or be absent.

- Hypomyelination (disproportionately thin myelin sheaths) may be due to:
  - dysmyelination (failure of the proper development of myelin in developing animals)
  - myelin loss (demyelination)
  - remyelination (see Figure 6.12).
- Hypermyelination may be observed in the peripheral nervous system (PNS). Excessively thick myelin sheaths are usually related to repeated attempts at remyelination.
   Hypermyelination is a rare observation in animals, e.g. hypertrophic neuropathy in Tibetan Mastiffs (Cooper et al., 1984).

Disorders of myelination can be primary, but are often secondary to other processes including endocrine (e.g. diabetes mellitus), compressive and inflammatory diseases.

#### Schwann cell changes

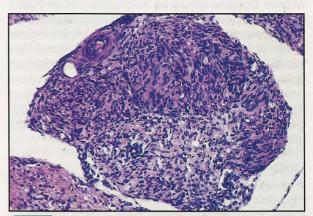
Specific pathological alterations of Schwann cells may be due to developmental abnormalities, storage diseases, toxins, immune dysfunction or neoplasia (malignant nerve sheath tumours).

#### Support tissues

The supporting tissues of nerves (meninges of proximal nerve roots, peri/endoneurium, blood vessels) may also reflect disease. Hypertrophy of these structures is the most common abnormality. Hypertrophy may reflect the duration of the process or may be secondary to an infiltrate.

#### Infiltration

The presence, distribution and nature of an infiltrate are important observations in understanding the disease process. Infiltrates generally reflect inflammation (Figure 6.13) or invasion by tumour cells. Special techniques may be required for detailed characterization of specific features (e.g. subtyping of lymphoma).



Nerve root affected by *Neospora canis*. The nerve has become thickened and there is an increased density of nuclei suggesting a cellular infiltrate. H&E stain, original magnification X60.

# Summary of interpretation

The information from examination of the biopsy tissue may lead to a specific diagnosis. Often, however, changes are non-specific and may support the presence and nature of disease, without revealing a specific cause, as well as suggesting a prognosis, i.e. if there is endoneurial fibrosis, marked nerve fibre loss and no regeneration, there is often a poor prognosis for recovery.

#### **Brain biopsy**

The veterinary neurologist relies heavily on computed tomography (CT) and magnetic resonance imaging (MRI) when diagnosing intracranial diseases. However, while imaging will give some information about the nature of a lesion (such as size, location and relationship to other intracranial structures), it can only provide, at best, circumstantial evidence as to the underlying pathology. Frequently the differential list for a lesion found on imaging the brain includes sterile inflammation, infection and neoplasia. Furthermore, ancillary tests such as cerebrospinal fluid taps and electroencephalography are often unhelpful in distinguishing between these diagnoses. Given that different pathological processes require different therapeutic approaches and carry different prognoses, a definitive diagnosis should be sought, and this may require pathological examination of the tissue involved.

# **Indications**

Generally, tissue may be biopsied for one of three reasons:

- To provide a diagnosis to determine optimal treatment
- To provide a diagnosis to give a more accurate prognosis for the patient

 As part of therapy (either excisional biopsy in an attempt at curing the disease, or debulking to alleviate clinical signs).

Those lesions that are most suited to biopsy are those that are easily visible on imaging studies, particularly with contrast medium. This includes the majority of brain tumours, as well as lesions of an inflammatory and/or infectious nature, especially if the inflammation is focal, superficial and well defined. Examples include the focal form of granulomatous meningoencephalitis (GME), abscesses and localized encephalitis/meningitis (Figure 6.14).

# Lesions well suited to intracranial biopsy

Most tumours situated in superficial locations: meningioma; astrocytoma; oligodendroglioma; ependymoma; metastatic adenocarcinoma; some lymphoid tumours

Lesions caused by inflammatory diseases that are focal in nature: focal GME; abscesses; some forms of encephalitis

#### Lesions poorly suited to intracranial biopsy

Tumours in deep seated areas: medulloblastoma within the cerebellum/medulla; other tumours in thalamus, hypothalamus or brainstem

Vascular tumours: choroid plexus papilloma; metastatic haemangiosarcoma

Vascular lesions: cerebral haematoma; cerebrovascular malformation

Diffuse lesions: diffuse GME; some lymphomas; gliomatosis cerebri

**6.14** Suitability of various lesions for intracranial biopsy.

Diffuse lesions are less suited to biopsy as selection of representative sample areas is more difficult and the tissue taken may not yield a definitive diagnosis. Examples of lesions less suited to biopsy include some tumours (e.g. gliomatosis cerebri and some forms of lymphoma), diffuse GME and viral encephalitides (Figure 6.15). It should also be remembered that biopsy is

more risky with lesions which are likely to bleed significantly. This includes some tumours (e.g. choroid plexus papilloma) and lesions involving the cerebral vasculature (e.g. vascular hamartoma).

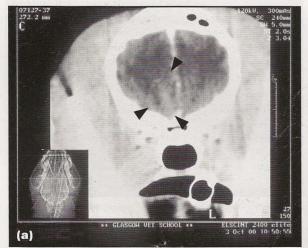
#### Tissue selection

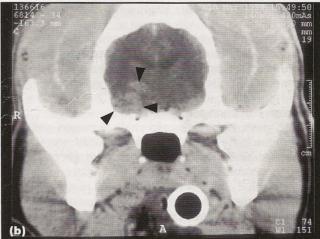
When performing biopsies of intracranial lesions, it is important to select areas that are likely to contain the most active (and therefore representative) pathological processes. The presence of hypodense or hypointense areas within a lesion following contrast administration is suggestive of necrosis, fluid accumulation or possibly oedema. Samples taken from these areas may consequently be non-diagnostic and yield little more than fragments of necrotic brain tissue. Samples taken from regions that can be enhanced with contrast media, however, are more likely to yield tissue with a good vascular supply, and consequently represent those areas that are involved in the active pathological process. These principles are particularly important when performing stereotactic needle biopsy, where the volume of tissue provided is limited and the chance of sampling non-representative tissue is relatively high. When sampling deep lesions, even needle biopsy may prove a risk. It has been recommended in humans that only one needle biopsy sample be taken from the brainstem or other high-risk areas. This is to decrease the risk of haemorrhage and compromise of adjacent vital structures such as the cardiovascular and respiratory centres (Kondziolka et al., 1998). Consequently, selecting the site from which the sample is to be taken in order to maximize the diagnostic yield becomes critical.

#### **Techniques**

#### Open craniectomy

Open craniectomy is a relatively common procedure, usually performed in order to carry out excision or debulking of a lesion, although it may also be undertaken for other reasons, such as decompression





Examples of lesions unsuitable for biopsy. (a) Granulomatous meningoencephalitis. Post-contrast CT scan shows patchy, mild contrast uptake diffusely (arrowheads) with white matter oedema but no obvious focus to target. (b) Intraparenchymal haemorrhage. Following contrast administration this CT scan appeared similar to pre-contrast scans with minimal uptake of contrast medium but a patchy, poorly defined area of hyperintensity (arrowheads).

following cranial trauma. Many parts of the brain are accessible via open craniectomy, including the olfactory, frontal, temporal, parietal and occipital lobes (via a frontal sinus, lateral or extended lateral approach) and the cerebellum (via suboccipital or caudotentorial approach). Lesions located deep to the surface of the brain, which are not visible at surgery, can be localized accurately using ultrasonography. However, in general, these approaches do not allow access to deeper parts of the brain, such as the thalamus, or brainstem.

#### Needle biopsy

Needle biopsy may be performed either 'freehand', usually to access very superficial lesions through a burr hole created following imaging and localization (with or without the assistance of ultrasonography), or using a stereotactic frame to guide the needle, again following imaging and localization (Figure 6.16). Freehand fine needle aspirations may also be performed on superficial lesions. Stereotactic biopsy is generally performed using a side-cutting brain cannula. The cannula is a blunt-ended needle with an inner and outer sheath, both of which contain a lateral window. Once the cannula is introduced into the region to be sampled, tissue is withdrawn into the inner sheath using gentle suction applied via a syringe attached to the end of the cannula. The inner sheath is then rotated through 180 degrees in relation to the outer sheath, the sharp edges of the lateral window of the inner sheath thereby excising the brain fragment within the inner sheath using a guillotine action. The sample is then collected by withdrawing the inner sheath from the outer sheath. Stereotactic needle biopsy has been used in human neurosurgical institutions extensively over the past two decades, and stereotactic frames and biopsy systems have now been developed for use with dogs and cats, although they are not yet widely available (Koblik et al., 1999a; Moissonnier et al., 2002). Stereotactic biopsy allows access to lesions in parts of the brain that are inaccessible via open craniectomy, and is generally regarded as being a safe and reliable technique, with figures for morbidity and mortality in humans ranging from 2-6% and 0-2.3%, respectively (Burger and Nelson, 1997; Kondziolka et al., 1998). Stereotactic



6.16

Leksell stereotactic frame. This is one of the most commonly used frames for image-guided needle biopsy in human patients. (Courtesy of Elekta UK.)

biopsy may also allow aspiration of fluid from fluid-filled lesions, and be used to introduce treatment agents into lesions, bypassing the blood—brain barrier.

#### Choice of technique

The decision on which method to use is dictated primarily by the facilities available to the neurosurgeon. Other factors that need to be considered include the appearance of the lesion on CT or MR imaging, the location of the lesion (intra-versus extra-axial) and the neurological status of the patient (Figure 6.17). If the neurological status of the patient is poor and raised intracranial pressure is suspected, a craniectomy and biopsy may be performed to allow decompression and alleviation of clinical signs, in addition to providing tissue for diagnosis. Lesions in deep structures, however, may be difficult to biopsy via an open craniectomy. This particularly applies to lesions in the deep grey matter of the forebrain (e.g. thalamus, hypothalamus) or brainstem (e.g. medulla oblongata). In this situation, stereotactic needle biopsy may be preferable, if available, as it causes less damage to vital structures. With lesions that are thought to be very vascular, based on their imaging characteristics, conventional biopsy obtained via a craniectomy may be more desirable than a needle biopsy as haemorrhage can be controlled intraoperatively (Figure 6.17).

Technique	Advantages	Disadvantages
Open craniotomy	Allows decompression for patients with deteriorating neurological status Requires less specialized equipment and facilities Allows control of haemorrhage intraoperatively Provides large tissue samples	Only able to access superficial lesions  More invasive with higher morbidity
Needle biopsy	Minimally invasive with low morbidity and mortality Allows sampling of lesions in deep areas of the brain	Requires specialized equipment Does not allow decompression for patients with deteriorating neurological status Provides smaller tissue samples Does not allow control of haemorrhage intraoperatively

6.17

Advantages and disadvantages of brain biopsy.

# Complications

#### Craniectomy

Complications associated with conventional craniectomy have been well described. The majority of these are the result of damage to important structures during surgery, either through direct trauma or following secondary haemorrhage and/or infarction. Primary damage that occurs during surgery may be followed by more significant and progressive secondary damage. This secondary damage is mediated by biochemical, vascular and inflammatory events, all of which contribute to the end results of neuronal and glial necrosis, ischaemia or infarction, cerebral oedema and raised intracranial pressure. Ultimately, if this process is not interrupted or reversed, cerebral or cerebellar herniation may result, leading to death of the patient. Less severe damage may result in postoperative seizures, which may necessitate long-term anticonvulsant therapy (Kostolich and Dulish, 1987). As with any open surgical procedure, iatrogenic infection may occur following surgery, which is serious and commonly fatal. A significant complication reported with intracranial surgery is aspiration pneumonia associated with prolonged periods of recumbency and possible megaoesophagus; this may be seen with brainstem lesions (Fransson et al., 2001).

#### Needle biopsy

Stereotactic biopsy is also associated with complications, although these are generally rare. The most common problem is haemorrhage caused by the biopsy as this may lead to significant neurological deficits and may be life-threatening. To prevent this the biopsy trajectory must be planned carefully in order to avoid major blood vessels and care should be taken if imaging findings suggest the lesion to be highly vascular (e.g. choroid plexus papilloma) (Figure 6.18). Additionally, it is important to maintain normal systemic blood pressure during surgery, as hypertension in humans has been reported to increase the risk of haemorrhage following biopsy. As with conventional craniectomy, postoperative imaging is recommended following needle biopsy to detect haemorrhage. Close monitoring of the patient's neurological status should also be performed for 48 hours following the procedure and scanning should be repeated if any deterioration in the level of consciousness occurs. In rare cases, a craniectomy

6.18 CT scan of a choroid plexus papilloma following the injection of contrast medium. Note that there is marked contrast medium uptake resulting in the extremely hyperdense appearance of the lesion (arrowed). This is consistent with a highly vascular lesion.

may be required to alleviate raised intracranial pressure or to adequately control haemorrhage. Other complications reported in dogs include:

- · Transient worsening of clinical signs
- Seizures
- · Cardiac arrythmias
- Epistaxis
- Hypercapnia
- Apnoea.

A rare complication reported in humans is 'seeding' of a tumour along the needle tract. Overall morbidity and mortality rates in dogs and cats are higher than in humans, and range from 12–26% and 7–8%, respectively (Koblik *et al.*, 1999b; Moissonnier *et al.*, 2002). In addition, it should be remembered that due to the small volume of tissue sampled during needle biopsy procedures, it is fairly common to obtain a non-diagnostic sample, especially if a non-representative part of the tumour is targeted. It is therefore extremely helpful to perform cytology or to preserve frozen sections during the procedure to ensure that a representative sample has been obtained (see below).

# Tissue handling and processing

Samples obtained by conventional biopsy or stereotactic needle biopsy may be submitted for either frozen sections or smear cytology in addition to routine histopathological examination. Fine needle aspirate samples are generally submitted for conventional cytological examination. Fixation of biopsy samples in 10% BNF is most common, allowing standard H&E and a range of immunohistochemical stains to be used. Samples submitted for snap-freezing in liquid nitrogen can be subjected to specific immunohistochemical stains if a particular disease is suspected and facilities for snapfreezing are available.

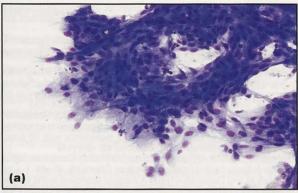
As standard formalin fixation and paraffin embedding is relatively time-consuming, a portion of the sample may be examined intraoperatively to provide a provisional diagnosis. The aims of intraoperative evaluation are two-fold:

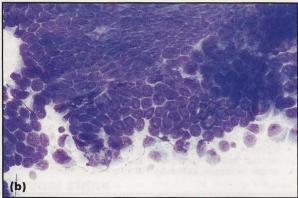
- To confirm the diagnostic value of the sample in order to minimize the number of samples taken
- To provide a provisional diagnosis that facilitates patient management in the early postoperative period.

The most common form of intraoperative diagnosis utilizes frozen sections, which requires specialized equipment and the ability to snap-freeze samples in liquid nitrogen soon after their acquisition. Turnaround time from sample submission to staining and examination is approximately 20–30 minutes.

An alternative to frozen sections is the use of smear preparations. Smear preparations are created by placing the sample on one glass slide and, applying pressure, quickly and firmly 'smearing' the sample with the end of a second glass slide. Smear preparations are rapid to perform, with a turnaround time of approximately 90 seconds depending on the stain used. Rapid stains such as Romanovsky-type (e.g. Diff-Quik) or toluidine blue may be used, as well as standard H&E staining.

Smear preparations have also been shown to be useful in confirming the presence of disease and differentiating inflammation from neoplasia (Long *et al.*, 2002). Viewing smears at low power often provides valuable information as different lesions smear in characteristic ways (Figure 6.19). In the case of tumours, while they may suggest a particular type of neoplasm, smear preparations may be less useful in providing an accurate grading of malignancy due to the small tissue sample examined. The reader is referred to the comprehensive report by Vernau *et al.* (2001) for a description of the cytological appearance of those lesions characterized in the dog.





Smear cytology characteristics of intracranial tumours at low power. (a) Meningioma. Note the cohesive nature of this tumour and the tumour cells adhering to branching capillaries. Diff-Quik stain; original magnification X50. (b) Metastatic carcinoma. Note the appearance of sheets of tumour cells and 'moulding' of cell nuclei to each other. Diff-Quik stain; original magnification X50.

#### Interpretation

The histological characteristics of most intracranial lesions in dogs and cats have been well described in several texts (Summers *et al.*, 1995). Several important features of the brain biopsy, which may help to achieve a diagnosis, are listed below:

- Number of cells
- · Presence of abnormal cells (neoplastic cells)
- Presence of inflammation (either diffusely within the brain parenchyma or clustered around blood vessels)
- Appearance of brain cells (e.g. chromatolytic neurons, hypertrophic astrocytes)

- Appearance of background tissue (e.g. oedema, necrosis)
- Presence of special features (e.g. inclusion bodies).

#### Number of cells

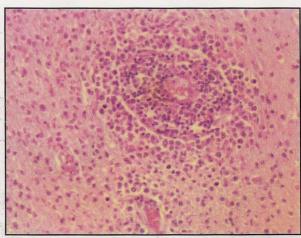
The number of cells in a given part of the brain may give an important clue to the underlying pathology. Hypercellularity may occur with an increase in the population of brain cells normally resident in the brain (usually astrocytes, oligodendrocytes or microglia), an increase in inflammatory cells migrating into the brain from elsewhere, and an increase due to proliferation of neoplastic cells. It may be difficult to distinguish between inflammation and neoplasia on the basis of cell number alone.

#### Abnormal cells

Abnormal cells are most commonly neoplastic. These may be of a single morphological type or may vary widely in shape and size. More uniform cells are suggestive of a well differentiated tumour, while variation in size and shape suggests a more malignant, poorly differentiated tumour. Other hallmarks of neoplasia may also be seen, including mitotic figures, vascular changes (predominantly endothelial hyperplasia) and necrosis.

#### Inflammation

Inflammatory cells may arise from normal brain tissue or may migrate into the brain from blood vessels. Cells within the normal brain that have inflammatory functions include astrocytes and microglia. An increase in number of either of these is often seen with certain types of intraparenchymal inflammation. Inflammation may also be characterized by the presence of large numbers of inflammatory cells surrounding blood vessels (Figure 6.20); these cells most commonly consist of a mixture of lymphocytes, macrophages and plasma cells, and the majority enter the brain via the bloodstream.



Biopsy sample taken at craniotomy showing marked perivascular cuffing with mononuclear inflammatory cells, predominantly lymphocytes and plasma cells, in granulomatous meningoencephalitis. H&E stain; original magnification X50.

#### Brain cell appearance

The population of cells normally resident in the brain may also exhibit changes. Neurons undergoing degeneration may show pale areas within the cell body with loss of the normal granular Nissl substance and eccentric nuclei; this change is termed chromatolysis. Neurons undergoing hypoxic or ischaemic damage may appear shrunken and brightly eosinophilic. Astrocytes may also display a variety of appearances in certain lesions. Large, swollen astrocytes containing eosinophilic material within their cytoplasm are termed gemistocytes and these may be a feature of chronic inflammation or of neoplasia (gemistocytic astrocytoma).

# Background tissue appearance

The neuropil may show areas of vacuolation and pallor comprising oedema, or may show areas of necrosis, becoming degenerate and fragmented. Necrosis occurs as the result of inadequate perfusion of the tissue and can be a component of many different disease processes including neoplasia.

#### Other features

Specific features may also be identified within sections that suggest a particular diagnosis. These include the inclusion bodies seen with viral encephalitis and the presence of intracellular vacuoles containing storage products in certain storage diseases.

# Summary of interpretation

In some circumstances interpretation may not give a definitive diagnosis or could be misleading. This occurs particularly when an area of a lesion is sampled that is not representative of the underlying pathology. For example, the periphery of certain lesions, including tumours, may show non-specific reactive inflammation with hypercellularity due to an increase in the number of astrocytes that are reactive in nature. If this area is sampled, it may be difficult to conclude whether the lesion is inflammatory or neoplastic in nature as benign astrocytic tumours may appear to be very similar to non-specific reactive inflammation.

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# Seizures

# Michael Podell

#### Introduction

The approach to and treatment of seizure disorders in small animals is similar in many respects to the treatment of various other ailments in veterinary medicine: an antecedent historical problem arises, a proper diagnosis is made to confirm the condition, and therapy is initiated to treat the underlying disease or signs of the disease. However, important differences arise specific to the diagnosis and treatment of seizure disorders. First, a specific underlying aetiology is often not identified. Secondly, the clinician must often make a therapeutic decision based on historical accounts alone. Thirdly, treatment is often initiated when the pet is otherwise normal, with little ability to predict frequency of seizure recurrence. Finally, the quality of life of both the pet and the owner during the interictal period must be balanced with the ability to limit the severity, frequency and duration of future seizure events. This chapter is designed to help clinicians to understand the variables for consideration in the treatment of seizure disorders in the cat and dog.

# **Clinical signs**

Classification of seizures and epilepsy into a universally accepted, coherent and relevant scheme for clinicians has been an ongoing dynamic process in human epilepsy since the early 1980s. The standardized classification scheme for seizures and epilepsy established by the International League Against Epilepsy (ILAE) in the 1980s (Commission for ILAE, 1981, 1989) provided the first basis for a taxonomic foundation for an analytical approach in the diagnosis and treatment of epilepsy. This classification scheme is restricted by the following limitations:

- The reliance on the clinician's ability to classify seizure types based on the presence of 'impaired consciousness'
- The reliance on electroencephalographic (EEG) features to classify seizure type
- The difficulty in distinguishing between an 'idiopathic' disorder of confirmed undetermined aetiology versus a 'cryptogenic' cause of highly suspect morphological disease of the brain (Engel, 2001).

The goal is to attempt to piece together a rational categorization for use in small animal epileptic patients adapted from the recent recommendations of the ILAE Task Force on Classification and Terminology (Engel, 2001). The purpose is to establish a common-ground mode of communication to allow diagnostic and therapeutic data to be tabulated for clinical outcome measures. The proposed new diagnostic scheme consists of five levels or axes (Figure 7.1) as proposed by Engel (2001).

#### Axis 1: Ictal phenomenology

Seizure:

Epileptic seizure

Non-epileptic episodes

Status epilepticus

# Axis 2: Seizure type

Self-limiting:

Focal

Sensory

Motor

Elementary

**Automatisms** 

Generalized

Tonic-clonic

Clonic

Myoclonic

Atonic

Clustered or continuous (status epilepticus):

Focal

Motor: epilepsia pars continua

Sensory: aura continua

Generalized

Reflexive: Precipitating stimuli present

#### Axis 3: Syndrome

Familial epilepsies

Idiopathic epilepsies:

Focal

Generalized

Symptomatic epilepsies

Probable symptomatic epilepsies

Reflex enilensies

Epileptic encephalopathies (progressive neurological dysfunction)

Myoclonus epilepsies

Proposed diagnostic scheme (five axes) for dogs and cats with epileptic seizures. (Adapted from Engel, 2001.) (continues)

# Axis 4: Aetiology Idiopathic Symptomatic Probably symptomatic Axis 5: Impairment from the epilepsy Temporary: Motor Sensory Other Permanent: Motor Sensory Other Other

7.1 (continued) Proposed diagnostic scheme (five axes) for dogs and cats with epileptic seizures. (Adapted from Engel, 2001.)

# Axis 1: Ictal phenomenology

A seizure can be defined as a non-specific, paroxysmal, abnormal event of the body. An epileptic seizure is the clinical manifestation of excessive and/or hypersynchronous abnormal neuronal activity in the cerebral cortex (Podell, 1996). Thus, an epileptic seizure has a specific neural origin. Absolute confirmation that a seizure is epileptic may be difficult as it requires simultaneous observation of behavioural and EEG changes. As a result, historical information is often used to diagnose an epileptic seizure. The clinical features of epileptic seizures can be separated into four components (Engel, 1989; Podell, 1996).

- The prodrome is the time period prior to the onset of seizure activity. Owners report that they can 'predict' the onset of their pet's seizures by behaviours exhibited during this time, such as increased anxiety-related behaviours (i.e. attention-seeking, whining), reluctance to perform normal activity patterns, or increased hiding (especially in cats).
- The aura is the initial manifestation of a seizure. During this period, which can last from minutes to hours, animals can exhibit stereotypical sensory or motor behaviour (e.g. pacing, licking), autonomic patterns (e.g. salivating, urinating, vomiting) or even unusual psychic events (e.g. excessive barking, increased or decreased attention-seeking).
- The ictal period is the actual seizure event, manifested by involuntary muscle tone or movement, and/or abnormal sensations or behaviour, lasting usually from seconds to minutes.
- The postictal period follows the actual seizure and can last from minutes to days. During this time an animal can exhibit unusual behaviour, disorientation, inappropriate bowel and/or bladder activity, excessive or depressed thirst and appetite, or actual neurological deficits of weakness, blindness and sensory and motor disturbances. The latter problems are known as Todd's paralysis and are often an indicator of a focal, contralateral cortical epileptic focus. Often owners observe only the postictal period as evidence that their pet has had a seizure.

Regardless of cause, a patient's epileptic seizures may be recurrent over time or may occur as a single event. If the patient has a chronic brain disorder characterized by recurrent epileptic seizures, then that patient has *epilepsy*. Note that neither the term seizure nor epilepsy connotes the underlying aetiology of the disorder.

Status epilepticus can be defined as a state of continuous seizure activity lasting for 30 minutes or longer or repeated seizures with failure to return to normality within 30 minutes (Engel, 1989) (see Chapter 19). Epilepsia partialis continua is a continuous focal seizure involving the motor cortex (Engel, 2001). Although not well documented by EEG in animals, the typical manifestations include facial muscle movements with 'chewing gum' activity, repetitive eye and/ or lip twitching or myoclonic jerking of limb muscles.

Several other paroxysmal 'episodes' of altered behaviour, body movement or neurological status may mimic epileptic seizures (see Chapter 17). Distinguishing these 'episodes' from epileptic seizures is just as important, as an incorrect diagnosis could lead to failure to identify another serious medical condition, the administration of unnecessary medication to the patient, or undue emotional and financial strain on the owner. Some common causes include syncope of cardiac origin, metabolic-related weakness (e.g. transient hypoglycaemia, endocrine diseases) and acute toxicities. One helpful distinguishing feature is the lack of a post-ictal period with these 'episodes'. With syncope, a rapid return to consciousness or ability to walk within seconds to a minute is typical, although some animals will urinate during or immediately after the event. Neurological episodes that are not epileptic seizures may be acute vestibular attacks (with ataxia, falling, rolling, etc.), narcoleptic events (sudden loss of consciousness with excitement) or a myasthenia gravis crisis (rapid loss of the ability to walk) (see Chapter 17).

# Axis 2: Seizure type

Seizure types are first classified as being:

- Self-limiting (isolated)
- · Clustered (two or more within 24 hours)
- · Continuous (status epilepticus).

Within each category, seizures are divided into being either focal or generalized. Focal seizures are the manifestation of a discrete, epileptogenic event in the cerebral cortex (Cascino, 1992). The focal nature of this seizure type is associated with a higher incidence of focal intracranial pathology (Podell et al., 1995). Focal seizures can be elementary motor seizures, commonly seen as facial muscle twitching, or manifested by more abnormal behavioural disorders. Progressive involvement of the facial, neck and/or shoulder or limb muscles is known as a 'Jacksonian' march seizure event. More complex behaviour patterns with focal seizures will include impaired consciousness, often with bizarre behavioural activity. Previously termed complex partial or psychomotor seizures, these events are now classified as automatisms, or automotor seizures (Engel, 2001). Animals may show 'fly-biting'

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behaviour patterns, become aggressive without provocation, howl incessantly, become restless or exhibit a variety of motor disturbances. Cats may show a variety of abnormal behaviours or motor signs, including drooling, hippus, excessive vocalizations or random, rapid running behaviours indoors. Whenever a focal seizure is suspected, the clinician should be suspicious of a focal cerebral disturbance and plan the diagnostic work-up accordingly.

Generalized seizures are subdivided into tonic-clonic, clonic, myoclonic, atonic or absence types. The terms convulsive (*grand mal*) and non-convulsive (*petit mal*) seizures are no longer in use. Generalized seizures originate from both cerebral hemispheres from the start, or progress secondarily from focal seizures (Figure 7.2) (Engel, 1989; Berendt and Gram, 1998). Unlike focal seizures, generalized seizures are not necessarily associated with focal cerebrocortical disease.

# Axis 3: Syndrome

By definition, a syndrome is a group of signs or characteristics that defines a particular abnormality. Epilepsy syndromes are not well defined in veterinary medicine, though familial epilepsies are now being identified with segregation analysis. A number of dog breeds have been identified with either proven or highly suspect familial epilepsy; these include Belgian Tervuerens (Famula and Oberbauer, 2000), Vizslas (Patterson *et al.*, 2003), Keeshonds (Hall and Wallace, 1996), Retrievers (Jaggy *et al.*, 1998) and Shetland Sheepdogs (Morita-*et al.*, 2002). The vast majority of epileptic syndromes in dogs are idiopathic in nature.

# Axis 4: Aetiology

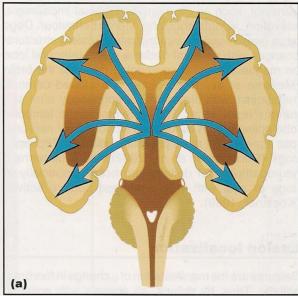
The differential diagnosis of epileptic seizures due to underlying brain disease can be divided into four main aetiological categories: idiopathic; symptomatic; probable symptomatic (previously termed cryptogenic); and reactive.

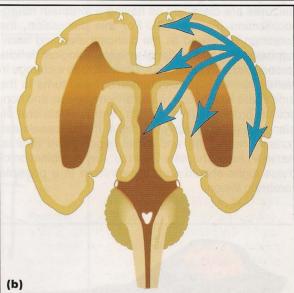
- Idiopathic epilepsy implies that no underlying structural brain lesion is present and is presumed to be genetic in origin.
- Symptomatic epilepsy is the result of an identifiable structural lesion of the brain.
- Probable symptomatic epilepsy ('cryptogenic') is believed to be the result of a structural lesion of the brain that is not identifiable.
- Reactive epileptic seizures are due to metabolic or toxic disease and therefore are not classified as an aetiology for epilepsy, as the brain returns to normal once the underlying abnormality is corrected.

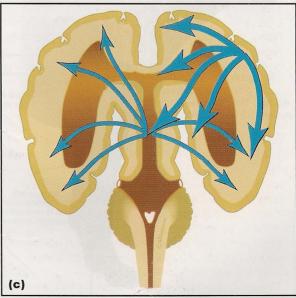
The differential diagnoses for these categories are discussed below.

# Axis 5: Impairment from the epilepsy

Inclusion of signs that are associated with epilepsy allows evaluation for persistence of functional and structural neurological changes with associated seizures. The majority of signs in cats and dogs are







7.2 Schematic representation of the abnormal origins of (a) generalized, (b) focal and (c) focal progressing to generalized seizure discharges.

transient, such as disorientation, visual impairment, salivation, incontinence and altered behaviour. Dogs have been found to demonstrate transient structural changes with cerebral oedema of the temporal lobe on magnetic resonance imaging (MRI) of the brain (Mellema *et al.*, 1999) along with altered cerebral metabolism with proton MR spectroscopy after seizures (Neppl *et al.*, 2001). Symptomatic temporal lobe epilepsy with associated hippocampal neuronal loss appears not to be present in idiopathic epileptic dogs (Buckmaster *et al.*, 2002). More permanent neuropathological deficits can occur, especially in dogs or cats with very prolonged seizure activity (Koestner, 1989).

# **Lesion localization**

Seizures are the manifestation of a change in forebrain activity. Thus, by default, all animals with epileptic seizures are classified as having a forebrain neurolocalization (Figure 7.3). For this discussion, the forebrain is defined as the diencephalon and telencephalon as one functional unit. Neurological deficits associated with forebrain lesions include a change in behaviour, wide circling patterns, head turns to the side of the lesion, contralateral hemiparesis and conscious proprioceptive deficits, and contralateral vision loss (cranial nerve II), facial muscle weakness (cranial nerve VII) and facial hypoalgesia (cranial nerve V) (see Chapters 2 and 8). Any combination of these signs should alert the clinician to a possible forebrain lesion.



7.3 Lesion localization for seizure disorders; the forebrain consisting of the cerebrum and the diencephalon is highlighted.

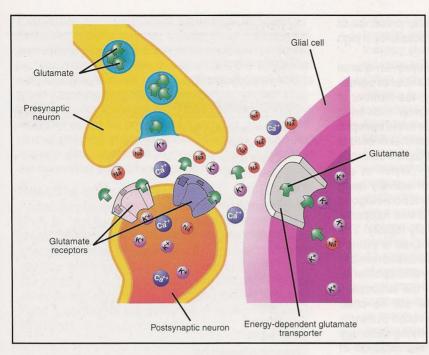
# **Pathophysiology**

Epilepsy represents a heterogeneous disease consisting of diverse aetiologies, electrophysiological and behavioural seizure patterns, and responses to pharmacological intervention. As such, the pathogenesis of epilepsy is multifactorial. Genetically determined seizure susceptibility factors play a crucial role in the brain's response to triggering or precipitating factors. also known as the seizure threshold. The seizure threshold in humans has been shown to decrease during sleep (in particular stage 2 sleep), where the hypersynchrony of sleep facilitates both the initiation and propagation of focal seizures in the parietal and occipital lobes (Herman et al., 2001). Seizures in these individuals may be activated from unrecognized changes in neuronal activity, or intrinsic neurochemical transmission, or by environmental stimuli or stresses that do not cause seizures in the normal brain.

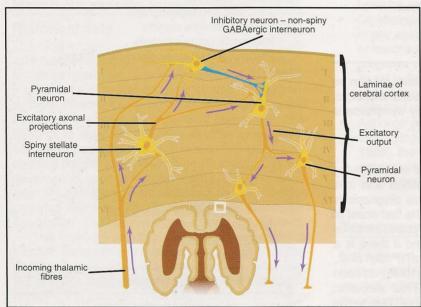
A basic tenet in the mechanism of epilepsy is the presence of an imbalance in excitatory and inhibitory neurotransmission. A seizure develops when the balance shifts towards excessive excitation. Recently, much research has been focused on the role of glutamate and its receptor complex, the *N*-methyl-D-aspartate receptor (Lipton and Rosenburg, 1994). Glutamate is the principal excitatory neurotransmitter in the brain, playing an important role in the modulation of cognitive, motor, memory and sensory functions of the central nervous system (CNS) (Figure 7.4). The overabundance of excitatory influences in the immature brain is also important in the developmental neuronal plasticity of the mammalian nervous system (Lipton and Rosenburg, 1994; Veliskova *et al.*, 1994).

As the brain matures, the balance of excitation and inhibition becomes a finely tuned process. Conditions leading to excessive excitation or loss of inhibition will lead to depolarization of neurons without normal regulatory feedback mechanisms. The result is a paroxysmal depolarization shift of a neuronal aggregate. In response to this sudden change in brain activity, local surrounding inhibitory zones are established to try to prevent the spread of this epileptogenic activity (Figure 7.5). Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain involved in this process. If inhibition is unsuccessful, other neuronal aggregates are excited through thalamocortical recruitment, intrahemispheric association pathways or interhemispheric commissural pathways. Successful recruitment of a critical number of areas with synchronized depolarization will then lead to a seizure (Figure 7.6).

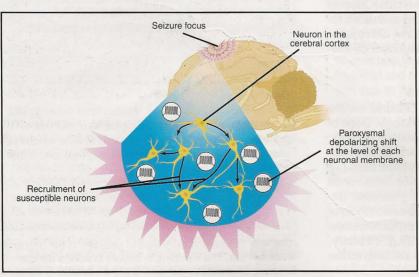
Recently, ion channel mutations have been linked to a variety of epilepsies considered idiopathic in humans. The majority of genes identified to date for human idiopathic epilepsy are inherited disorders of ion channels, known as channelopathies (Noebels, 2003). Each ion channel is a protein complex comprising several subunits. Excessive influx of sodium, blockade of efflux of potassium or altered calcium flux can lead to repetitive neuronal firing. Specific functional genetic mutations have been identified for each of these ion channels in humans (Noebels, 2003). Although similar mutations



7.4 Schematic representation of the glutamate receptors in the central nervous system generally responsible for excitation of associated neurons.



Schematic representation of the neuronal circuitry in the cerebrum responsible for feed-forward excitation and feed-forward inhibition. An imbalance in the levels of excitation and inhibition can lead to seizure discharges. (Modified from March, 1998)



7.6 Recruitment of groups of neurons undergoing a 'paroxysmal depolarizing shift' can be responsible for extension of the seizure focus.

have yet to be identified in animals, the presence of familial epilepsy in the dog makes this possibility a high likelihood in the near future.

In the initial stages of idiopathic epilepsy, an animal may possess only a single or limited number of epileptic foci. With recurrent seizure activity, the number of cells with an intrinsic pattern of high spontaneous firing activity ('pacemaker cells') will increase in the epileptic focus. An increase in the number of pacemaker cells is highly correlated with an increase in seizure frequency in experimental models of epilepsy (Wyler et al., 1978). Furthermore, a mirror focus of actively firing epileptogenic neurons may develop in a homologous region on the opposite hemisphere. If this happens, the number of epileptic foci can multiply rapidly. The significance of these changes is that, as a patient continues to seizure, there will be an increased number of areas of the brain that are randomly and spontaneously able to initiate a seizure. Thus, the successful medical management of this patient will be challenged. Prevention of this sequence relies primarily on the early identification of the underlying aetiology of the seizure disorder, followed by the initiation of appropriate medical therapy (see below).

# **Differential diagnosis**

The differential diagnosis of epileptic seizures can be divided into four main aetiological categories: idiopathic; symptomatic (or secondary); probably symptomatic (cryptogenic); and reactive (Figure 7.7).

# Idiopathic epilepsy

Idiopathic epilepsy (IE) is diagnosed if no underlying cause for the seizures can be identified and it is presumed to be of genetic origin. This diagnosis is most common in purebred dogs with the first onset of seizures between the ages of 1 and 5 years, a normal interictal neurological examination, and if there is a lengthy initial interictal period (>4 weeks) (Podell *et al.*, 1995). As stated above, a genetic basis for IE has been reported in numerous dog breeds. True idiopathic epilepsy is much less common in the cat due to the more diverse genetic background of most cats (Quesnel *et al.*, 1997). As such, all cats should be evaluated for underlying reactive or secondary seizures with appropriate diagnostic testing before a diagnosis of idiopathic epilepsy is made.

# Symptomatic epileptic seizures

Symptomatic, or secondary, epileptic seizures are the direct result of structural forebrain pathology. Dogs of any age or breed may develop secondary epileptic seizures. Younger dogs are more prone to developmental and encephalitic diseases, while older dogs (>7 years of age) are more likely to develop intracranial neoplasia. As expected with underlying cerebral pathology, these animals are more likely to exhibit focal or multifocal neurological deficits. However, focal lesions in 'silent' cortical areas of the brain (e.g. olfactory, pyriform and occipital lobes) may have seizures as the only neurological problem.

# Idiopathic

Channelopathies [7]

Other genetic diseases [7]

# Symptomatic (or secondary)

Developmental anomaly [8]

Hydrocephalus

Cortical dysplasia

Lissencephaly

Neoplasia [8]

Extra-axial: meningioma, bone tumours

Intra-axial: glial tumours, metastasis

Intraventricular: ependymoma, choroid plexus tumours

Infectious [10]

Viral

Bacterial

Rickettsial

Fungal

Protozoal

Parasitic

Inflammatory diseases [10]

Granulomatous meningoencephalitis

Eosinophilic meningoencephalitis

Breed-specific meningoencephalitis

Other corticosteroid-responsive inflammatory diseases

Toxicity

Lead [8]

Organophosphates

Ethylene glycol

Traumatic [19]

Vascular [8]

Ischaemic

Thromboembolic

Idiopathic

Feline ischaemic encephalopathy

Haemorrhagic

Hypertension related

Coagulopathy

## Probably symptomatic (or cryptogenic)

Prior head trauma in patients with normal imaging

Postencephalitic seizures developing months to years later

Undetected hypoxic or vascular events of the brain post-anaesthesia In utero or birth trauma

#### Reactive

Organ failure

Hepatic [8]

Renal [8]

Electrolyte imbalance

Hypo- or hypernatraemia [8]

Hypocalcaemia [12]

Energy deprivation

Hypoglycaemia [8]

Thiamine deficiency [10]

7.7 Differential diagnosis of seizures in the dog and cat. The numbers in square brackets denote chapters where these conditions are discussed in detail.

# Probable symptomatic epileptic seizures

Probable symptomatic, or cryptogenic, epileptic seizures are believed to be due to an underlying unidentified brain disease. While this sounds like a somewhat nebulous disease category, it has particular implications when understanding why certain animals may be refractory to therapy. Examples of cases that may fit into this category would be prior head trauma in patients with normal imaging, postencephalitic seizures developing at a later date, undetected hypoxic or vascular events of the brain after anaesthesia, or birth trauma.

# Reactive epileptic seizures

Reactive epileptic seizures are a reaction of the normal brain to transient systemic insult, toxic reaction or physiological stresses. Animals of any age may be affected. Smaller-breed dogs are more predisposed to develop seizures secondary to portosystemic shunts at a younger age. Typically, a higher seizure frequency will occur initially until the underlying metabolic or toxic insult is corrected, but evidence of systemic illness is often present concurrently.

# **Neurodiagnostic investigation**

# Historical data

The most important component in approaching a seizure case is acquiring a thorough and accurate history. Enquiries regarding the seizure event should address a description of the event, time of day, duration and postictal effects. The purpose is to establish overall frequency, seizure type, patterns of occurrence, relationship to daily activity (e.g. exercise, sleep) and severity of post-ictal effects. It is recommended that a charting technique measuring seizure frequency and severity should be developed to aid in objective evaluation of future therapeutic success. Owners should be provided with a calendar to record the frequency and description of all observed and suspected seizures.

The interictal status of the dog's cerebrocortical function (between seizures and after the postictal period) can be evaluated by asking questions concerning the animal's behaviour, vision, gait and sleep/wake patterns. For example, if the dog is more withdrawn or attention seeking, showing any unusual episodes of aggression or irritability, or fails to follow simple commands, then a structural cerebral problem should be suspected. Likewise, subtle gait disturbances (stumbling up or down the stairs), visual disturbances (occasionally bumping into objects on one side) and restless sleep patterns may indicate forebrain problems.

#### Diagnostic evaluation

The sequence of diagnostic testing for any animal with seizures should proceed from the least invasive to the most invasive (and expensive) diagnostic modality.

 A complete blood count (CBC), biochemistry panel (including blood glucose), urinalysis and blood pressure measurement should be performed for all animals being evaluated for an epileptic seizure. For dogs, additional testing is based upon the age, breed, seizure type, seizure frequency and neurological examination findings.

- Dogs <1 year of age and those being initiated on hepatic metabolized antiepileptic drug (AED) therapy should also be evaluated for hepatic disease with a serum bile acid study.
- Other individual tests for toxin exposure (e.g. plasma lead, serum cholinesterase assay), parasitic or rickettsial infection, or systemic illness are based on the clinical picture at the time of presentation.
- For cats, the basic screening should include a retroviral screen for feline leukaemia and feline immunodeficiency virus and testing for serum antibodies to *Toxoplasma gondii*. Testing for the virus causing feline infectious peritonitis is not recommended, as the correlation between a positive titre and active CNS infection is low.
- All dogs aged 7 years or older with an initial onset of seizures, regardless of the seizure pattern or frequency or neurological examination, should undergo advanced imaging of the brain with MRI or computed tomography (CT). Due to the high incidence of symptomatic epilepsy in cats, the author recommends that advanced imaging of the brain be performed in all epileptic cats.
- Cerebrospinal fluid (CSF) analysis is recommended in any animal with multifocal neurological deficits or lesions observed on MRI or CT scans. The presence of an abnormal CSF analysis has been found to be highly associated with the presence of underlying brain parenchymal lesions as detected on MR images (Bush et al., 2002).
- Although EEG analysis is beneficial in identifying underlying epileptic foci in the dog (Berendt et al., 1999), the overall usefulness of this test for determining diagnosis and treatment has yet to be proven.

# **Treatment**

Management of epilepsy in cats and dogs often requires a lifetime commitment by owners. The owner must be willing to medicate their pet several times per day, travel to emergency clinics at unpredictable times, follow up with periodic re-evaluations and diagnostic testing, and watch their pet carefully for adverse effects of therapy. The balance between quality of life and therapeutic success is often a key issue for an owner to continue treating their pet. Despite all of the time, financial and emotional commitment, a significant portion (up to 40%) of dogs may still continue to have seizures (Lane and Bunch, 1990). Thus, proper client education is critical in preparing owners for understanding their pet's condition and the potential associated lifestyle changes.

The decision to start AED therapy is based on a number of factors, including type, aetiology, severity and postictal effects. Overall, the earlier that therapy is initiated in epilepsy, the better will be the long-term success rate with monotherapy, as already documented in human epilepsy therapy (Kwan *et al.*, 2000). Monotherapy should be started in the dog or cat in any of the following situations:

# Chapter 7 Seizures

- Symptomatic epilepsy is diagnosed
- · Status epilepticus has occurred
- Two or more isolated seizures occur within a 6-month period
- Two or more cluster seizure events (two or more seizures within a 24-hour period) occur within a 12-month period
- · The first seizure is within 1 week of a trauma
- Severe or unusual postictal effects are present (e.g. prolonged blindness, aggression).

Selection of the appropriate AED is based upon the efficacy, pharmacokinetic properties and adverse effects of that drug. AEDs can be classified into three broad mechanistic categories that decrease either the seizure onset or the spread of seizures (Figure 7.8):

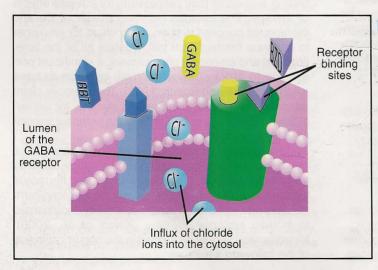
- Enhancement of inhibitory processes via facilitated action of GABA (Figure 7.9)
- · Reduction of excitatory transmission
- · Modulation of membrane cation conductance.

Unfortunately, several limitations exist in the selection of AEDs for use in veterinary medicine, including toxicity, tolerance, inappropriate pharmacokinetics and expense (Podell, 1998). In the past, many of the AEDs useful in humans could not be prescribed for small animals, due either to inappropriate pharmacokinetics (too rapid an elimination) or to potential hepatotoxicity. The result was that the most commonly used AEDs in veterinary medicine were from the same mechanistic category, that of enhancing inhibition of the brain. However, newer AEDs with alternative mechanisms of action are now available, allowing a broader selection of treatment options.

The efficacy and safety profiles of AEDs are determined in large part by their pharmacokinetic properties. Drugs that are the easiest to use by the general population are ones that have the most favourable pharmacokinetic properties (Bourgeois, 2000). Ultimately, an AED with the most desirable pharmacokinetic profile has complete bioavailability, is available as a parenteral formulation, and has an

Drug	Mechanism of action					
	Decrease se	izure onset	Decrease seizure spread			
	Enhanced Na+ channel inactivation	Enhanced GABA activated CI <sup>-</sup> conductance	Reduced current through Ca <sup>2+</sup> channels	Reduced glutamate- mediated excitation		
Phenobarbital		++	+	+		
Potassium bromide		++ a				
Felbamate	teren provinciale (	+	Distriction and U.S.	++		
Benzodiazepines		++				
Gabapentin	+	++ <sup>b</sup>	+	(+) character talk (		
Topiramate	+	+		+		
Zonisamide	+	Salah Isani	++	Emilia lessolai.		
Levetiracetam		++ b	ta heli gio bia	Luss as analytic		

7.8 Summary of the mechanism of action of several currently available antiepileptic drugs. <sup>a</sup> Competitive displacement of chloride through activated GABA receptors. <sup>b</sup> Indirect GABA receptor activation via increased GABA activity. + = secondary mechanism. ++ = postulated primary mechanism.



7.9 Schematic representation of a GABA<sub>A</sub> receptor in the central nervous system generally responsible for increasing local chloride levels and causing a surrounding inhibition. The receptor can be bound by barbiturates and benzodiazepines. BBT = barbiturate molecule; BZD = benzodiazepine molecule; GABA = gamma-aminobutyric acid.

elimination half-life suitable for daily or twice-daily dosing, linear elimination kinetics, no autoinduction of enzymatic biotransformation, no pharmacokinetic interactions with other drugs, rapid brain penetration, a volume of distribution with a single compartment, low and non-saturable protein binding, and no active metabolites. The ideal AED has not yet been formulated for any species.

In general, monotherapy is still the recommendation for new-onset epilepsy. The use of a single AED has the advantages of offering: no drug interactions; more predictable pharmacokinetic and pharmacodynamic properties; and less potential for adverse effects. It is also less expensive. Successful treatment with one drug can be enhanced by ensuring that owner and patient compliance, therapeutic serum concentration, maximal tolerance (maximal dose without further adverse effects) and appropriate duration are met. Not all epileptic pets can be controlled with a single AED and some patients require multiple medications for successful treatment. The following is an overview of the more commonly available AEDs available for use in the dog and cat.

# Specific antiepileptic drug treatment in the dog

Figure 7.10 summarizes the AEDs available for the treatment of dogs.

#### **Phenobarbital**

Phenobarbital, a phenyl barbiturate, has the longest history of chronic use of all AEDs in veterinary medicine, as it is a relatively inexpensive, well tolerated drug that can be administered two to three times per day and has well documented success in preventing seizures (Farnbach, 1984; Schwartz-Porsche *et al.*, 1985; Parent and Quesnel, 1996).

# Pharmacology

Phenobarbital has a high bioavailability, being rapidly absorbed within 2 hours and with a maximal plasma concentration obtained within 4–8 hours after oral administration (Ravis *et al.*, 1989). Almost one-half of the drug is protein bound. The majority of phenobarbital is metabolized by the liver, with approximately one-third excreted unchanged in the urine. Phenobarbital is

Antiepileptic drug	Clinical pharmacology				Therapeutic range	Initial dose	Efficacy	Major possible adverse effects
	T <sub>1/2</sub> (h)	Tss (d)	Vd (l/kg)	Prot Bd (%)				
Phenobarbital <sup>a</sup> (Ravis <i>et al.</i> , 1989)	24–40	10–14	0.8	40	20-40 mg/dl	2.5 mg/kg q12h	Generalized seizures	Sedation; polydipsia; polyphagia; liver disease; induces p450 system
Potassium bromide <sup>a</sup> (March <i>et al.</i> , 2002)	15–20 days	100– 200	0.40	0	Monotherapy: 2000–3000 mg/l With phenobarbital: 1500–2500 mg/l	40 mg/kg/day 30 mg/kg/day	Generalized seizures	Sedation; weakness; polydipsia; GI irritation; pancreatitis
Felbamate <sup>a</sup> (Adusumalli <i>et al.</i> , 1992)	5–6	1–2	1.0	25	25–100 mg/l	20 mg/kg q8h	Partial seizures	Blood dyscrasia; liver disease; induces p450 system
Gabapentin <sup>a</sup> (Radulovic <i>et al.</i> , 1995)	2–4	1	0.2	0	4–16 mg/l	30-60 mg/kg/day b (divide q12h or q8h)	Generalized and partial seizures	Sedation
Clorazepate <sup>a</sup> (Forrester <i>et al.</i> , 1990)	5–6	1–2	1.6	85	20–75 μg/l (nordiazepam)	2–4 mg/kg/day (divide q12h)	Add on: generalized and partial seizures	Sedation; withdrawal seizures
Topiramate	20–30	3–5	0.65	15	2–25 mg/l	2–10 mg/kg q12h b	Add on: generalized and partial seizures	Gl upset; irritability
Zonisamide <sup>a</sup> (Leppik, 1994)	15–20	3–4	1.5	50	10–40 μg/ml	5-10 mg/kg/day	Add on: generalized and partial seizures	Sedation, ataxia, loss of appetite
Levetiracetam <sup>a</sup> (Isoherranen <i>et al.</i> , 2001)	4-6	1–2	0.5	< 10	ND	5-30 mg/kg q8-12h b	Add on: generalized and partial seizures	Not greater than placebo in humans

Summary of the antiepileptic drugs available for use in dogs. <sup>a</sup> Clinical pharmacology data presented for dogs. <sup>b</sup> Gradual incremental dosing recommended. ND = not determined; Prot Bd = protein binding; T<sub>1/2</sub> = elimination half-life; Tss = approximate time to steady-state; Vd = volume of distribution.

an auto-inducer of hepatic microsomal enzymes (p450 system), which can progressively reduce the elimination half-life with chronic dosing.

#### Side-effects

Overall, phenobarbital is well tolerated at therapeutic serum concentrations in the dog. Idiosyncratic drug reactions to phenobarbital can be either behavioural or biochemically mediated. Behavioural changes, such as hyperexcitability, restlessness or sedation, may occur after starting treatment with the drug, but they appear not to be dose-related and resolve typically within 1 week. A more serious idiosyncratic reaction is development of an immune-mediated neutropenia or thrombocytopenia in dogs (Jacobs et al., 1998), as well as anaemia. Typically, this reversible blood dyscrasia will occur within the first 6 months of dosing. Rare acute, idiosyncratic hepatotoxic reactions may also be present, as evidenced by a rapid elevation of alanine aminotransferase (ALT) and abnormal dynamic bile acid levels. The drug should be stopped immediately if either neutropenia or dramatic elevations in ALT are noted, and the animal should be loaded with an additional AED, such as potassium bromide (see below). Phenobarbital may also be a risk factor for the development of superficial necrolytic dermatitis in dogs (March et al., 2004).

Chronic adverse historical effects usually revolve around polydipsic and polyphagic behaviour. As a result, dogs may develop psychogenic polydipsia with associated polyuria. The most common serum biochemical change with chronic phenobarbital therapy is an elevation of serum alkaline phosphatase (Bunch et al., 1985). These changes can occur as soon as 2 weeks after starting therapy. Neither endogenous adrenocorticotropic hormone (ACTH) nor exogenous response to ACTH is altered by phenobarbital dosing (Dyer et al., 1994). Moreover, phenobarbital does not interfere with the low-dose dexamethasone suppression test, regardless of dose or treatment time (Foster et al., 2000). Serum total and free thyroxine (T4) concentrations may be low in dogs treated with phenobarbital, resulting in a mistaken diagnosis of hypothyroidism (Kantrowitz et al., 1999).

Three serious and potentially life-threatening complications can occur with long-term phenobarbital therapy:

- With time, physical dependence on the drug does develop. Withdrawal seizures can occur as serum phenobarbital concentrations decline to between 15 and 20 μg/ml
- There may be the development of functional tolerance to the drug. Functional tolerance is the loss of drug effectiveness due to changes in drug—receptor interaction, change in drug distribution into the brain, or progression of an underlying disease state
- Potentially the most life-threatening complication is drug-induced hepatotoxicity. Hepatotoxicity to primidone (which is metabolized predominantly to phenobarbital), either alone or in combination with other AEDs, has been shown to occur in

experimental and clinical conditions in dogs (Bunch *et al.*, 1985; Poffenbarger, 1985).

Documentation of a serum phenobarbital concentration >35 μg/ml had the highest correlation with the development of hepatotoxicity (Dayrell-Hart *et al.*, 1991). All animals on chronic phenobarbital therapy should have a routine biochemistry panel performed every 6–12 months to monitor for the development of chronic hepatotoxicity. A bile acid tolerance test should be performed to evaluate liver function if ALT levels suddenly increase or if the serum albumin level starts to decrease.

# Administration and monitoring

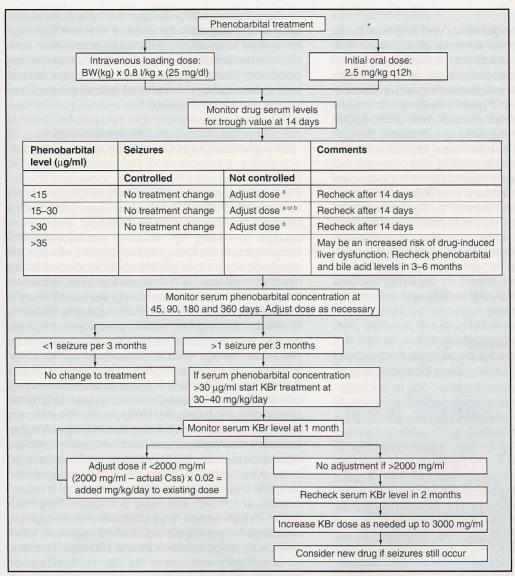
The appropriate starting dose of phenobarbital for dogs is 2.5 mg/kg orally q12h (see Figures 7.10 and 7.11). An intravenous loading-dose can be used to produce a rapid rise in serum blood concentration. This starting dose is the only time to use a weight-based dosage. All future adjustments should be based on serum drug concentrations. The objectives of monitoring trough serum concentrations of any AED are:

- To determine whether a therapeutic value is present at the time when the lowest serum concentration is present, as dogs will be most likely to seizure at this time
- To record that serum concentration fluctuates within the established therapeutic range for that drug when chronically administered (steady-state concentration)
- · To prevent toxic effects from occurring
- To individualize therapy.

Serial serum trough phenobarbital concentrations should be evaluated at: 14, 45, 90, 180 and 360 days after the initiation of treatment, at 6-month intervals thereafter, if the pet has more than two seizure events between these times, and at 2 weeks after a dosage change. Although blood level fluctuations may not be dramatic throughout the day in dogs with steady-state concentrations (Levitski and Trepanier, 2000), blood samples are best taken in the early morning, prior to dosing, in a fasted dog, to increase consistency in comparison with published information, maintain consistency in interpretation and remove diurnal or dietary-induced fluctuations of absorption (Maguire *et al.*, 2000).

Adjustments in AED dosages are done either to enhance the effect or to reduce the adverse effects. The most efficacious and safe trough therapeutic phenobarbital range for the dog is 15–30  $\mu$ g/ml. An optimal starting level is between 20 and 25  $\mu$ g/ml. Increments of 5  $\mu$ g/ml are beneficial if seizures are occurring at an equal frequency or worsening after 30 days of therapy. Adjustments of the trough phenobarbital levels can be calculated with the following formula:

(Desired concentration/Actual concentration) x total mg phenobarbital per day = Oral daily dose of phenobarbital (mg)



Algorithm for use of phenobarbital and potassium bromide (KBr) in the dog. a The dose of phenobarbital should be increased by 10-25%. b The dose of phenobarbital should be cautiously increased or a second drug, such as KBr, should be given. The formula used to calculate the phenobarbital dose adjustments is as follows: Desired concentration/Actual concentration x (mg phenobarbital per day) = Oral daily dose in mg.

A 20% or greater drop in the trough serum concentration is often an indicator of poor administration compliance. Overall, phenobarbital is an AED that can provide excellent seizure control in idiopathic epileptic dogs with careful serial monitoring of trough serum drug concentrations.

# Potassium bromide

Potassium bromide is the recommended add-on AED of choice in the dog. Concomitant potassium bromide and phenobarbital administration decreased seizure numbers and severity in the majority of dogs in several studies, with seizure-free status ranging from 21% to 72% of all treated dogs (Schwartz-Porsche and Jurgens, 1991; Podell and Fenner, 1993; Trepanier *et al.*, 1998). In general, many canine refractory idiopathic epileptic patients may benefit from potassium bromide. By allowing a reduction of the use of drugs metabolized by the liver, potassium bromide therapy may also reduce the incidence of hepatotoxicity.

# **Pharmacology**

In the USA bromide is typically given as the inorganic salt potassium bromide, usually as a solution of 200-250 mg/ml dissolved in double-distilled water. In the UK several formulations are available. Potassium bromide is a known mucosal irritant and capsules may result in gastric irritation due to the direct contact of a concentrated amount of the drug with the gastric lining. A starting dose of 40 mg/kg/day potassium bromide is slowly metabolized in the dog, with a median elimination half-life of 15.2 days, resulting in achievement of median steady-state concentrations of 2450 mg/l (March et al., 2002); apparent total body clearance was 16.4 ml/kg/ day and volume of distribution was 0.40 l/kg. Steadystate concentrations fluctuate between dogs, most likely due to individual differences in clearance and bioavailability. Dietary factors also alter serum drug concentrations, with high-chloride diets resulting in excessive renal secretion and lower serum concentrations (Trepanier and Babish, 1995).

#### Side-effects

Potassium bromide is generally well tolerated in the dog. The most common adverse effects seen with potassium bromide and phenobarbital combination therapy are polydipsia, polyphagia, increased lethargy, and mild ataxia with increasing serum concentration. Pancreatitis and gastrointestinal intolerance have also been reported (Gaskill and Cribb, 2000). Potassium bromide may cause skin problems (bromoderma), although no substantiated reports exist currently. Intoxication to the point of stupor is rare but pelvic limb ataxia, weakness and altered behaviour are more likely with serum concentrations >3000 mg/l. Caution should be used in treating dogs with underlying renal insufficiency, due to reduced renal elimination (Nichols et al., 1996). Therapy for potassium bromide intoxication consists of intravenous normal saline administration to enhance renal excretion. Careful monitoring is advised, as dogs may become more susceptible to seizure activity with lowering of the serum concentration.

# Administration and monitoring

Potassium bromide can be administered at a starting dose of 40 mg/kg/day when used as sole therapy or 30 mg/kg/day when used as an add-on drug to phenobarbital. Potassium bromide serum concentrations should be measured at 1 month and at the first steady-state concentration (approximately 8–12 weeks). The recommended goal is to achieve steady-state trough serum concentrations of 25  $\mu$ g/ml for phenobarbital and 2000 mg/l for potassium bromide. The range is highly individualized according to the seizure pattern of each dog. Further reductions in phenobarbital can be attempted if a seizure-free period is maintained for 6 months. The dosage is adjusted according to the formulae given below.

# Combined therapy

For concomitant phenobarbital and potassium bromide treatment, the new maintenance dose can be calculated as follows (where Css = steady-state concentration):

(Target Css – Actual Css) x (Clearance/Bioavailability) = (2000 mg/l – Actual Css) x 0.02 = mg/kg/day added to existing dose

#### Monotherapy

Potassium bromide monotherapy is recommended in dogs with underlying liver disease, less frequent seizure activity (<3 per year) and in some dogs with idiopathic epilepsy. The use of potassium bromide monotherapy is not recommended for high initial frequency seizure activity, if secondary epilepsy is present, or if unwarranted adverse effects persist (e.g. weakness, extreme polydipsia). The oral monotherapy starting dose is 40 mg/kg/day. Oral loading dosing can be accomplished with a dose of 800 mg/kg divided into equal doses q4h over 1 day, but may result in gastric upset. Alternatively, a dose of 400–600 mg/kg divided over 4 days in addition to the maintenance dose has been suggested.

Dogs treated with potassium bromide alone should have serum drug concentrations at or above 2500 mg/l for optimal seizure control. Gradual increases in dose allow for better adaptation to the drug. For monotherapy potassium bromide-treated patients, the new maintenance dose can be calculated as follows (where Css = steady-state concentration):

(Target Css – Actual Css) x (Clearance/Bioavailability) = (2500 mg/l – Actual Css) x 0.02 = mg/kg/day added to existing dose

#### **Felbamate**

Felbamate is a dicarbamate with proven ability to block seizures induced by a variety of methods. Felbamate is believed to increase seizure threshold and prevent seizure spreading by reducing excitatory neurotransmission in the brain. Neuroprotective effects have also been shown through this ability to alter excitatory neurotransmission. In human clinical trials, felbamate has been shown to be most useful as monotherapy in the treatment of uncontrolled partial epilepsy. The drug is metabolized by the hepatic microsomal p450 enzymes, with increased metabolism in younger dogs (Adusumalli et al., 1992). In dogs, the drug has a high bioavailability and protein-binding capability (see Figure 7.10 for dose). Effective control of focal seizure activity with documented therapeutic serum concentrations has been shown with felbamate therapy in dogs (Ruehlmann et al., 2001). Felbamate is a non-sedating drug. A higher incidence of aplastic anaemia and liver toxicity has been reported in humans, but these adverse effects have not been documented in dogs. Serial monitoring of the complete blood count and biochemistry panel is recommended at 1 month and every 3 months during treatment. Trough serum drug concentration is typically measured 1-2 weeks after initiation of treatment, with a therapeutic range between 25 and 100 mg/l. This drug is not currently available in the UK and needs to be imported on special licence.

# Gabapentin

Gabapentin is an interesting new AED whose mechanism of action is still not fully understood. Initially designed to mimic GABA in the brain, gabapentin can readily pass through the blood-brain barrier. Once in the brain, however, gabapentin does not mimic the pharmacological properties of GABA nor does it bind to GABA receptors. In preclinical studies, gabapentin effectively blocked seizures induced by a variety of proconvulsant methods. New evidence suggests that gabapentin may facilitate the extracellular transport of GABA out of cells to act on the GABA, receptor (Honmou et al., 1995). The dog is the only known species to partially biotransfrom the drug to N-methylgabapentin (Radulovic et al., 1995). A major benefit of the drug is that the parent and metabolite drugs are renally excreted; thus it will not induce drug-drug interactions with other AEDs with hepatic metabolism (e.g. phenobarbital).

At present, clinical human trials have shown gabapentin to be most useful as an add-on therapy in the treatment of medically refractory focal and generalized seizures. Dosing every 8 hours may be necessary due to the rapid elimination half-life. Lower starting doses with gradual adaptation over time (e.g. once daily for several days, then twice daily) are recommended to avoid excessive sedation, which is seen as a side-effect in many dogs (see Figure 7.10). Reduced doses may be needed in patients with renal insufficiency. Serum monitoring is not recommended as the drug has a very high therapeutic index and little drug—drug interaction. Preliminary clinical evaluation of this drug as an add-on therapy for refractory idiopathic epileptic dogs has recorded an improvement in seizure frequency in approximately 50% of cases (Platt et al., 2003). Gabapentin is particularly useful in epileptic dogs with underlying hepatic disease.

# **Topiramate**

Topiramate is a sulphamate-substituted monosaccharide with a mechanism of action of blockade of seizure spread by rapidly potentiated GABA activity in the brain (Petroff et al., 2001). In humans, topiramate is well absorbed and is primarily excreted renally as an unchanged drug. With a relatively long half-life of 20-30 hours, twice-daily dosing is recommended. With a relatively broad-spectrum activity against many seizure types and minimal adverse effects, topiramate is approved for use in both adult and paediatric human patients. Dosing ranges are between 25 and 50 mg/day per patient (Holland, 2001) but gradual dose titration is better tolerated (see Figure 7.10). The author has used topiramate most successfully in dogs with focal and generalized seizures that were unresponsive to phenobarbital and potassium bromide therapy.

# Zonisamide

Zonisamide is a substituted 1,2-benzisoxazole derivative that works by both blocking the propagation of epileptic discharges and suppressing focal epileptogenic activity (Ito et al., 1980). Pharmacokinetic information in the dog is limited to a very small population of normal Beagles (Walker et al., 1988). In general, zonisamide is well absorbed and has a relatively long half-life and high protein-binding affinity. The drug is highly concentrated in red blood cells, due to high binding to carbonic anhydrase and other red cell protein components (Patsalos and Sander, 1994). Zonisamide is hepatically metabolized and thus is influenced by concurrent administration of other similarly metabolized drugs. Broadspectrum antiepileptic activity has been reported against a variety of seizure types, with particular improvement in the treatment of adult myoclonus epilepsy (Henry et al., 1988). Major adverse effects in human patients include a higher incidence of renal calculi formation, sedation and gastrointestinal disorders.

Zonisamide can be an efficacious and well tolerated drug in the dog with recurrent generalized seizures refractory to phenobarbital or potassium bromide therapy. The major adverse effects include sedation, ataxia and inappetence. Phenobarbital dosages should be reduced by 25% at the time of starting zonisamide. A preliminary report demonstrated that dogs responded to treatment with a blood level close to 20  $\mu g/ml$  (Dewey et al., 2003). This drug is not currently available in the UK and needs to be imported on special licence.

# Levetiracetam

Levetiracetam is the S-enantiomer of the ethyl analogue of piracetam that has broad-ranging, unique and not completely known mechanisms of action against seizures. The drug is well absorbed but is more rapidly metabolized than other drugs in humans. The pharmacodynamic effect is believed to outlive the known halflife. Levetiracetam was the best tolerated of all new AEDs in human clinical trials (Cramer et al., 1999), with adverse reactions equal to that of placebo. Overall, this drug is proven to be a highly effective adjunctive therapy in humans to control partial seizures previously refractory to treatment (Cereghino et al., 2000). In the author's experience, the best response to this drug has been as an add-on medication in dogs exhibiting automatisms and generalized seizures. A dose range for dogs of 5-30 mg/kg q8-12h has been suggested.

# Lamotrigine

Lamotrigine is a novel drug that is chemically unrelated to current AEDs. Although efficacious in human epileptic patients, the drug is converted to a cardiotoxic 2-N-methyl metabolite in dogs (Wong and Lhatoo, 2000), which is not found in humans. This drug is not recommended for use in dogs (Figure 7.12).

#### Inappropriate

Toxicity

Phenytoin (hepatic)

Primidone (hepatic)

Lamotrigine (cardiac)

Vigabatrin (blood dyscrasia)

Inappropriate pharmacokinetics

Carbamazepine (short elimination half-life)

Phenytoin (short elimination half-life)

Oral diazepam (inability to achieve therapeutic serum concentration)

# Use with caution

Synergistic hepatic toxicity

Phenobarbital and:

Felbamate

Zonisamide

Withdrawal seizures

Phenobarbital

Clorazepate Felbamate

7.12

Antiepileptic drugs inappropriate for use in the dog.

# Benzodiazepines

Benzodiazepines are a class of AEDs that interact with specific CNS benzodiazepine receptors that activate the GABA $_{\rm A}$  chloride channel to hyperpolarize neuronal membranes (see Figure 7.9). Diazepam is the most widely used benzodiazepine in veterinary medicine and is best used for the treatment of emergency seizures by intravenous and per rectum administration (see below and Chapter 19). Chronic oral administration of diazepam is not recommended in the dog, due to the lack of effectiveness to stop seizures, the very short half-life, potential for increased hepatic enzyme

inhibition, physical dependence, and cross-tolerance preventing effective use of intravenous diazepam in stopping seizures in an emergency (see Figure 7.12). A long-acting benzodiazepine, clorazepate, is a diazepam pro-drug with more suitable pharmacokinetic properties for chronic use in the dog, but similar problems may arise as with chronic oral diazepam, especially the potential for severe withdrawal seizure activity (Scherkl *et al.*, 1989).

# Specific antiepileptic drug treatment in the cat

Figure 7.13 summarizes the AEDs available for the treatment of cats.

# Phenobarbital

As in the dog, phenobarbital is the recommended firstline AED in the epileptic cat (Parent and Quesnel, 1996). The pharmacokinetic properties are similar to those in the dog, with a more prolonged elimination half-life range. However, the cat is more sensitive to the sedative effects and eliminates the drug more slowly. Thus the therapeutic range is lower, typically between 10 and 20 µg/ml, and dosing can be highly individualized. Most cats can be treated with 1-2 mg/kg/day, with once-daily dosing, initially at night. Subsequent increases to twice-daily dosing can be instituted as needed. Idiosyncratic reactions include blood dyscrasias, dermatitis and persistent unusual behaviours. Predictable dose-dependent adverse effects include polydipsia, polyuria and polyphagia. More severe problems may include hepatotoxicity, although this has not been reported to date. Overall, phenobarbital can be used successfully in the cat with proper monitoring, as described for the dog.

# Benzodiazepines

Diazepam is recommended for cats refractory to phenobarbital as an alternative but not concomitant AED. The dose range is 0.5–2.0 mg/kg, divided two to three times per day. Gradual adaptation is necessary to prevent excess sedation. Diazepam is metabolized to the active metabolites, nordiazepam and oxazepam.

Trough serum nordiazepam concentration should be in the therapeutic range of 200–500 ng/ml. Potential complications include similar behaviour problems to those described for phenobarbital therapy, physical dependence and possible withdrawal seizure activity, and acute fulminant hepatic necrosis. The latter problem is an idiosyncratic reaction that can be fatal (Center et al., 1995). Therefore, all cats treated with diazepam should have liver enzymes monitored within the first week of therapy and again within one month. The drug should be discontinued if any liver enzyme elevation is observed.

Clonazepam is an alternative to diazepam in the cat, as it does not undergo hepatic microsomal metabolism, has a more prolonged elimination half-life and, therefore, may not produce an idiosyncratic hepatic reaction. The recommended starting dose is 0.5 mg once to twice daily. Clorazepate is another long-acting benzodiazepine that the author has used successfully, though the precise pharmacokinetic properties of this drug are not well understood in the cat. The recommended dose range is 3.75–7.5 mg orally q24h to q12h. Similar precautions as described for diazepam are necessary.

# Potassium bromide

Potassium bromide in cats is not recommended as a standard therapy, due to the relatively high prevalence of adverse respiratory problems (Boothe and George, 2002). Cats can develop a cough and more severe respiratory signs suggestive of an allergic asthmatic disease (Wagner, 2001). The author no longer recommends the use of potassium bromide in cats.

# Gabapentin

Gabapentin is a useful AED in the cat due to its exclusive renal excretion, similar to that in the dog. Cats, however, may exhibit increased sedation and will benefit from a gradual increment in dosing over 1–2 weeks. The author recommends starting at 5–10 mg/kg daily for 3–5 days, then increasing to twice daily. Further increases are dependent upon response to therapy. Both solution and capsular formulations of the drug are available. The drug can be used as both a monotherapy and add-on medication.

Antiepileptic drug	T <sub>1/2</sub> (h)	Therapeutic range	Initial dose	Major possible adverse effects
Phenobarbital	34–43	10–20 μg/ml	1–2 mg/kg/day	Sedation; ataxia; polyphagia with weight gain; thrombocytopenia; swelling of feet; facial pruritis
Diazepam	15–20	500-700 ng/ml	0.5-2.0 mg/kg/day (divided q12h or q8h)	Acute hepatic necrosis; sedation; ataxia
Potassium bromide	10 days	Variable	30 mg/kg/day	Bronchial asthma
Clonazepam	Unknown	As for diazepam	0.5 mg q24h to q12h	Acute hepatic necrosis; sedation; ataxia
Clorazepate	Unknown	As for diazepam	3.75–7.5 mg orally q24h to q12h	Acute hepatic necrosis; sedation; ataxia
Gabapentin	Unknown	Undetermined	5-10mg/kg/day	Sedation; ataxia

Summary of the antiepileptic drugs available for use in cats.  $T_{1/2}$  = elimination half-life.

# **Emergency treatment**

# Hospital emergency treatment for seizures

A rapid, reliable protocol for the emergency management of seizures in dogs and cats is provided in Chapter 19. The physiological seguelae of frequent or continuous seizure activity (status epilepticus) leading to increased intracranial pressure and neuronal necrosis include systemic arterial hypertension, loss of cerebrovascular regulation, disruption of the blood-brain barrier and cerebral oedema.

# At-home emergency treatment for seizures

The financial and emotional constraints of providing recurrent emergency therapy can be overwhelming for the owner and result in euthanasia of the animal. It is important to discuss methods by which the owner can provide emergency treatment for their pet at home if the animal is prone to cluster seizures. Diazepam per rectum (DZPR) therapy by owners of dogs with primary epilepsy and generalized cluster seizures has been associated with a significant decrease in the number of cluster seizure events in a 24-hour period, and a decrease in the total number of seizure events when compared with an identical time period without such therapy (Podell, 1995). As a consequence of this there was a significant decrease in the total cost in emergency care per dog, when compared with a similar period prior to the onset of use of DZPR. Pharmacokinetic studies of DZPR in normal dogs demonstrated that chronic phenobarbital therapy in the dog reduces total benzodiazepine concentration after intravenous and per rectum administration, presumably due to increased hepatic clearance of diazepam or its metabolites, oxazepam and nordiazepam (Wagner et al., 1998). Administration of DZPR at 2 mg/kg in dogs on chronic phenobarbital achieved effective plasma benzodiazepine concentrations >300 µg/l with minimal adverse effects. A dose of 1 mg/kg is recommended without concurrent phenobarbital therapy. This dose can be given up to three times in a 24-hour period but should not be given within 10 minutes of a prior dose. No information is reported for rectal AED therapy in the cat.

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# Coma, stupor and behavioural change

Rodney S. Bagley

# Introduction

The basis of life is the result of consciousness and awareness. Disorders of consciousness reflect a figurative and, in many instances, a literal threat to life itself.

Terms used to describe the state of inappropriate mental function between alert ('normal') and severe impairment (stupor or coma) are not well agreed upon in veterinary medicine. The following terms are in common use to describe changes both in consciousness and in behaviour.

- Consciousness refers to the state of awareness of the animal and is sometimes termed wakefulness.
- Alert describes an animal that pays attention to its surroundings and is quick to respond in a predictable fashion to external stimuli.
- Awareness refers to the ability to 'take account' of an object, but it does not imply assessment of the nature of that object.
- Depressed or obtunded decreased functional activity, mentally dulled.
- Stuporous unresponsive to normal environmental stimuli but responsive to painful stimuli.
- Comatose unresponsive to any stimuli.
- Behaviour the observable response a patient makes to a given situation.
- Cognition refers to the mental process of 'knowing', which includes perceiving, recognizing, judging and sensing an object.
- Dementia refers to a situation of impaired intellectual function involving memory and judgment as well as changes in personality. This may not be a term that can be used in veterinary medicine as memory and judgment are difficult qualities to assess in animals. A more useful term may be 'inappropriate'.
- Delirium mental disturbance marked by illusions, hallucinations, cerebral excitement, physical restlessness and incoherence.

Abnormalities in consciousness and cognition can result from a variety of intracranial disease processes. Normal intracranial nervous system function responsible for consciousness, however, is influenced by multiple extracranial body systems and organs. Disease or

dysfunction of these non-neurological body systems can indirectly alter the animal's willingness or ability to respond appropriately to a variety of endogenous and environmental stimuli. Disorders of consciousness and/ or behaviour, therefore, may result from many primary intracranial diseases, but may also reflect a variety of systemic disease states. In an animal with alterations of consciousness it is important to discern whether the inciting abnormality resides primarily within the intracranial nervous system, or is the result of non-nervous system disease. As disorders that tend to cause severe alterations in consciousness are often life-threatening, coma and stupor are considered emergency situations.

# **Clinical signs**

Behaviour and consciousness may be difficult to evaluate in veterinary patients and often assessment is based on information from the owner about the animal's behaviour within its usual environment.

# Altered consciousness

Clinical signs of alterations in consciousness range from subtle (e.g. an animal that is just less active than normal) to severe (e.g. comatose and unable to respond to any external stimuli) (deLahunta, 1983; Oliver et al., 1987; Chrisman, 1991; Oliver et al., 1997). The 'normal' state of an animal's consciousness is dynamic and dependent on a complex interaction between stimuli and response, which varies from individual to individual and in some cases, from moment to moment. Clinical assessments of consciousness, therefore, are often crudely categorized into general groups of responses (Figure 8.1).

Mental status	Clinical response		
Normal	Alert		
Inappropriate	Responses are not normal but the animal can respond to some environmental stimuli		
Stuporous	The animal is unresponsive to environmental stimulation but responsive to painful stimulation		
Comatose	The animal is unresponsive to both environmenta and painful stimuli		

8.1

Mental status categories of animals.

#### Normal

An animal is assessed as alert if they respond in a predictable fashion to a given stimulus. Normal animals that are alert are acutely aware of changes in their environment. They orient themselves to alterations in activity, sound and light. Unless the clinician is very familiar with the animal's normal personality and response to a range of environmental stimuli, subtle abnormalities of consciousness are difficult to determine. It is often only through questioning the owner to establish the 'normal' personality of the animal that subtle alterations of consciousness are elucidated.

# **Abnormal**

Animals with depressed consciousness tend to stay in one location, may sleep more than normal, and be less responsive to external stimuli such as light, touch and sound. These animals may not eat and drink appropriately (Nelson *et al.*, 1981; Bagley, 1994) and can progress from depression through stupor to coma.

- Abnormalities of cranial nerve reflexes and pupil reactivity, posture and proprioception may also be present with intracranial derangements (see Lesion localization).
- Decerebrate rigidity, where the animal has opisthotonus, extensor rigidity of all limbs and either stupor or coma, is present with severe midbrain lesions.
- In addition to altered levels of consciousness, patients may have concurrent respiratory, cardiovascular and pupillary changes that can be helpful in assessing the location and severity of the lesion.

Altered respiration: There are a number of abnormal respiratory patterns that can be present with alterations in consciousness. These patterns aid in lesion localization in humans (see below), although there are differing opinions as to whether the same rules are applicable to companion animals.

- Cheyne Stokes respiration is characterized by a
   waxing and waning depth of respiration with
   regularly occurring periods of hyperphoea and
   aphoea (Adams and Victor, 1989; Guyton and
   Hall, 1996). This is seen with bilateral cerebral or
   diencephalic disease.
- Biot's breathing is irregular periods of apnoea alternating with periods of 4–5 breaths of identical depth. This is seen with increased intracranial pressure (ICP).
- Central neurogenic hyperventilation is due to mesencephalic lesions. Tachypnoea to the point of panting is seen.
- Apneustic breathing occurs with pontine lesions and is characterized by periods of breathing and apnoea that are very short, with cycles of respiration consisting of only 1–2 breaths interposed with periods of apnoea.
- Ataxic breathing, with an irregular rate and rhythm, can be caused by caudal brainstem (medulla oblongata) lesions involving the respiratory centres.

Altered cardiovascular function: Alterations in hear rate and rhythm such as bradycardia and tachyarrthymias may be evident in animals with increased ICP and brain—heart syndrome, respectively (Shapiro, 1975; King et al., 1982; Kornegay, 1993; van Loon et al., 1993; Bagley, 1996 a,c). Animals with significant increases in ICP may also have systemic hypertension as an attempt to increase cerebral blood flow (see Chapter 20).

Altered pupil function: Pupillary changes may be present in animals with alterations in consciousness (Neer and Carter, 1987; Collins and O'Brien, 1990; Scagliotti, 1990). With bilateral, usually severe cerebrocortical disease, the pupils will often be smaller than normal (miotic). Two theories exist to explain this finding (deLahunta, 1983):

- 1. There is a bilateral central sympathetic system abnormality, possibly at the hypothalamus or brainstem level.
- 2. It is the result of the supratentorial structures normally exerting a negative influence on pupillary constriction. With supratentorial disease, upper motor neuron (UMN) influence over cranial nerve (CN) III function is lost and, therefore, the pupillary constrictor response becomes hyperresponsive (excessive parasympathetic tone).

If unilateral transtentorial brain herniation occurs the ipsilateral pupil may dilate and become non-responsive to light because of pressure exerted on CN III from the herniated parahippocampal gyrus (Kornegay *et al.*, 1983), or because of stretching of CN III with lateral or falcine herniation of the cerebral hemisphere. As the mesencephalon is further compressed or damaged, fixed mid-range or, in some instances, dilated pupils will result (deLahunta, 1983).

# Transient alterations in consciousness

Episodic or short-term loss of consciousness with periods of normal consciousness in between may be found with narcolepsy, syncope and seizures.

- Narcolepsy (excessive daytime sleepiness) is an episodic disorder that results in rapid progression to deep sleep, usually following some triggering stimulus such as eating (see Chapter 17).
- Syncope is a short, episodic loss of consciousness that results from transient cerebral hypoxia or anoxia. Syncopal episodes may mimic a seizure (see Chapter 7) or narcoleptic and/or cataplectic event. If hypoxia is prolonged, actual seizures may result and confound the clinical interpretation. Syncope is most often the result of a cardiorespiratory disorder (usually a bradyarrhythmia) and, therefore, attention should be given to the cardiorespiratory systems during the routine physical examination (Adams and Victor, 1989).

#### Behaviour

Both the presence and quality of consciousness is important. The quality of consciousness essentially governs the ability of the animal to behave normally (Parker, 1990). Normal behaviour is a generalization determined for a population of animals but is also very individual. Alterations in behaviour may include aggression, vocalization, excessive or abnormal sexual activity, changes in eating, chewing, drinking, urinating, defecating, as well as changes in personality. Frenzied activity and repeated unusual behaviour such as tail chasing or fly biting might also occur. Changes in behaviour in relation to stimulating events, such as after eating in animals with hepatic encephalopathy, may also be important clues to an underlying metabolic disease process.

Changes in behaviour may be due to structural or functional cerebral disease. A subgroup of the functional disorders, well described in human medicine, used to be termed psychoneuroses and later just neuroses. However, more recently, the term neuroses has been replaced by such terms as anxiety disorders, phobic states and obsessive-compulsive disorders. Animals can show behavioural abnormalities as a result of stress (stereotypical behaviour). This type of abnormality can be difficult to differentiate from those alterations in behaviour associated with abnormalities of cognition: however, they usually have a repeatable pattern of similar activity that can be terminated through interaction with the owner or clinician. In general, clues to an underlying behaviour problem may be suggested by whether the abnormality occurs when the owner (audience) is not present, the animal's movements can be interrupted and whether the abnormality occurs at a consistent time or in response to a consistent stimulus or context (e.g. the owners leaving or coming home). Animals whose episodic abnormality occurs only in the presence of the owner or an audience, and animals that can be interrupted from the activity or have the abnormality only in response to a specific stimulus are more likely to have a behaviour problem.

# **Lesion localization**

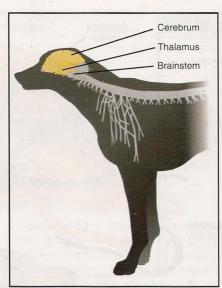
For an animal to be alert and oriented to its environment (i.e. normal level of consciousness and normal behaviour) neurons in the cerebral hemispheres, diencephalon and brainstem need to function appropriately (deLahunta, 1983; King, 1987; Colter, 1990; Chrisman, 1991; Oliver *et al.*, 1997) (Figure 8.2).

# Behaviour

Cognition, perception and emotional responses are controlled by the cortex and limbic system (see below) through connections with the thalamus and brainstem. Thus normal behaviour requires the complex interaction of numerous components of the cerebrum, thalamus and brainstem.

# Perception and cognition

Perception and cognition occur primarily through the activity of cortical neurons with input from additional



8.2

Lesion localization for coma and stupor; the cerebrum, diencephalon and brainstem are highlighted.

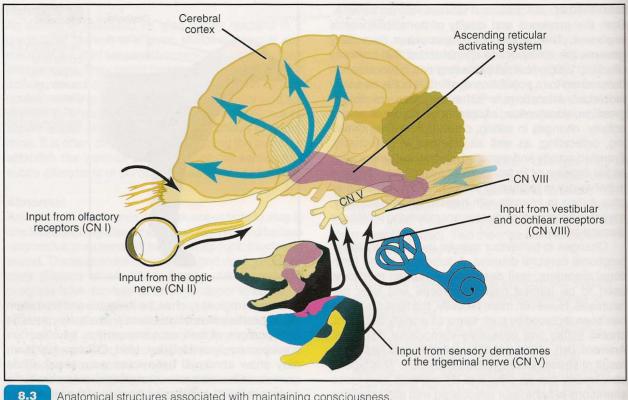
neurons in regions such as the thalamus and brainstem. With specific intracranial lesions animals may perceive only portions of their environment (i.e. hemi-inattention/hemi-neglect) (Holliday, 1991; O'Brien, 1993) and may show abnormal behaviours as a result. Thus, animals with unilateral supratentorial or forebrain disease turn their head toward the side of the lesion, and when walking, tend to turn or circle in that same direction. This is believed to result from a loss of cortical integration of sensory information from the contralateral side of the body. Other clinical signs of a unilateral supratentorial process can include:

- Seizures
- Behavioural abnormalities
- Lack of conscious recognition of touch and pain on one side of the face (contralateral to a unilateral lesion)
- Contralateral menace response deficits
- Deficits of conscious proprioception (contralateral to a unilateral lesion)
- The animal may pace compulsively but their gait is usually normal.

# Limbic system

The limbic system is associated with emotional and behavioural patterns in animals. The limbic system functions in the non-olfactory part of the rhinencephalon (the part of the brain once thought to be concerned entirely with olfactory functions). The name limbic (edge or border) is used because the nuclei that primarily make up the non-olfactory rhinencephalon lie in two incomplete rings on the medial aspect of the telencephalon at its border with the diencephalon. The term now includes other anatomically distant nuclei, such as those in the brainstem. The major structures of the limbic system include the amygdaloid, hippocampus and cingulate gyrus in the telencephalon, the thalamus and hypothalamus in the diencephalon and the reticular formation of the mesencephalon.

The function of the limbic system is to influence visceral motor activity, primarily through its influence on the hypothalamus. Neurons in this system receive



Anatomical structures associated with maintaining consciousness.

projections from the olfactory, optic, auditory, exteroceptive and interoceptive sensory systems. It is the portion of the brain in human beings that is involved in basic drives, sexual activity, emotional experiences. memories, fears and pleasures.

# Consciousness

Brainstem disease involving the ascending reticular activating system (ARAS) can significantly alter consciousness (deLahunta, 1983). The ARAS within the brainstem provides stimulatory input to the cerebral cortex via the diencephalon to maintain consciousness or wakefulness (Figure 8.3). The ARAS lies in the central portion of the brainstem from the medulla to the diencephalon. Many of these areas are ill defined and lie within the reticular formation. Afferent neurons to this area come from all pathways that project ascending sensory information. The ARAS projects to either the diencephalic reticular or hyposubthalamic reticular system. The diencephalic portion stimulates the entire cerebral cortex diffusely. The ARAS awakens the cortex to prepare it to receive sensory information. This system may allow for discrimination of stimuli, sorting out which stimuli to recognize or reject.

# Intracranial pathophysiology

Intracranial dysfunction may result from: a single primary lesion; secondary intracranial pathophysiological sequelae to a focal lesion (e.g. increases in ICP); or global CNS dysfunction as a consequence of extracranial systemic disease (Bagley, 1996a, b). Secondary pathophysiological alterations include, but are not limited to:

- Physical invasion and/or destruction of neurons
- Metabolic alterations in neuronal or glial cells
- Impairment of vascular supply to normal tissue (ischaemia or hypoxia)
- Impairment of autoregulation
- Haemorrhage
- Irritation (seizure generation)
- Obstruction of the ventricular system
- Oedema formation
- Production of physiologically active substances.

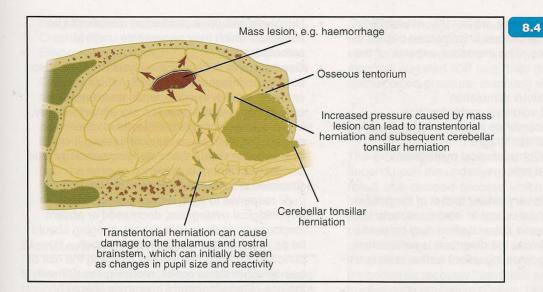
Many of these processes increase the relative volume within the intracranial cavity, ultimately affecting ICP. Increases in ICP result in decreases in cerebral blood flow leading to cerebral ischaemia and hypoxia. As a terminal consequence, increases in ICP lead to brain herniation and death (See Chapter 20 for further information on factors that affect ICP and cerebral blood flow).

There are several types of brain herniation (Kornegay et al., 1983) (Figure 8.4).

- 1. Transtentorial herniation occurs when the parahippocampal gyrus herniates caudally underneath the tentorium cerebelli. This causes compression of the midbrain and CN III resulting in loss of consciousness and dilated pupils unresponsive to light.
- 2. The most devastating type of herniation occurs when the caudal cerebellum herniates caudally

Various types of

brain herniation.



into the foramen magnum. The associated compression of the brainstem will affect the respiratory centres in the medulla oblongata and the animal usually ceases voluntary respiration. Treatment for this type of herniation, including both surgical and medical therapies, is usually unrewarding.

- Falcine herniation occurs when one cerebral hemisphere herniates laterally ventral to the falx cerebri as a result of a unilateral hemispheric lesion.
- 4. Herniation from a craniotomy site can also occur postoperatively.

# **Differential diagnosis**

Once abnormalities of consciousness and/or behaviour are established, it is important to determine whether the primary problem lies within the intracranial nervous system or is the result of dysfunction within a nonneural body system (Figure 8.5). Further discussion will be limited to important diseases within the CNS that result in abnormalities of consciousness and/or behaviour. It is taken for granted that any disease process that results in life-threatening changes in systemic, metabolic or cardiovascular function will ultimately affect consciousness in the terminal stages of the disease.

# **Neurodiagnostic investigation**

Depending on the localization of the disease, appropriate diagnostic tests (Figure 8.6) should be performed to rule in or out each disease on the differential diagnosis list. Sometimes the underlying disorder is evident (e.g. cranial trauma); however, all too often patients with stupor or coma can present a diagnostic challenge. If the patient presents in a coma, emergency evaluations of airway patency and vital signs including cardiac function and respiration should be undertaken, as for patients with head trauma (see Chapter 19).

Mechanism of disease	Specific diseases		
Degenerative	Inherited neurodegenerative diseases [8, Appendix 1 Lysosomal storage diseases [8, 15, Appendix 1]		
Anomalous	Hydrocephalus [8]		
Metabolic	Hepatic encephalopathy [8] Hypoglycaemia [8, 19] Electrolyte disturbances [8, 12] CNS perfusion [8] Hypothyroid myxoedema coma [8]		
Neoplastic	Primary – meningiomas, gliomas, choroid plexus papillomas, ependymomas, pituitary tumours [8] Metastatic – haemangiosarcoma, lymphoma, carcinomas [8] Local extension – e.g. multilobular osteochondroma (MLO)		
Nutritional	Thiamine deficiency [10]		
Idiopathic	Narcolepsy-cataplexy [17]		
Infectious	Viral, rickettsial, bacterial, protozoal, fungal, parasitic [10, 15]		
Inflammatory	Granulomatous meningoencephalitis [10] Necrotizing encephalitides (e.g. Pug dog encephalitis) [10] Steroid-responsive meningitis [13]		
Toxic	Lead [8] Ivermectin [8] Metronidazole [10]		
Traumatic	Head trauma [19] Intracranial haemorrhage [19] Subdural haematoma [19]		
Vascular	Arteriovenous malformation Infarction Feline ischaemic encephalopathy [8] Haemorrhage Hypertension		

Causes of coma, stupor and behavioural change.

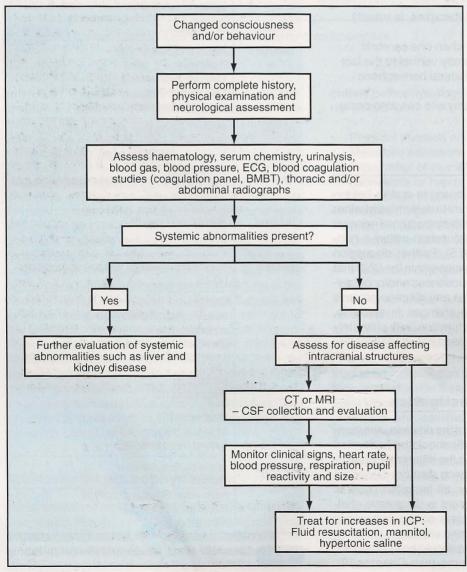
Although limited in many ways, the neurological examination of the stuporous or comatose patient is of crucial importance. The important aspects of the evaluation include:

- · Response to noxious stimulation
- · The presence of voluntary motor function
- Posture (e.g. decerebrate rigidity)
- · Pupil responsiveness to light
- · Eye movements (physiological nystagmus)
- · Segmental spinal reflexes.

This evaluation is very similar to that of the patient with severe head trauma and in some respects the modified Glasgow coma score system may be useful (see Chapter 19). Unless the diagnosis is established from the history (e.g. toxin ingestion) further testing is usually necessary.

 Routine laboratory analysis is essential; the minimal acceptable information should include packed cell volume (PCV), total protein concentration, BUN, electrolytes and glucose concentrations.

- Urinalysis and urine production rate should be assessed which may necessitate urethral catheterization.
- Cerebrospinal fluid (CSF) analysis is indicated to confirm an inflammatory lesion. Although such analysis is rarely specific, when assessed in conjunction with the patient's signalment, history, neurological signs and the results of other diagnostics such as serological assays, it can help to better define the underlying aetiology (see Chapter 3). If there is evidence or even a suspicion of increased ICP (anisocoria, lack of pupil response to light, reduced or absent physiological nystagmus, decreased or absent response to noxious stimulation), imaging should be performed prior to cisternal or lumbar puncture as these procedures increase the risk of herniation. In these cases, reducing the ICP with the use of mannitol and furosemide should be considered (see Chapters 19 and 20).
- Advanced imaging studies such as computed tomography (CT) or magnetic resonance (MR) imaging are strongly indicated to assess the



Algorithm for the diagnostic approach to patients with changed consciousness and/or behaviour. BMBT = buccal mucosal bleeding time; CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiography; ICP = intracranial pressure; MRI = magnetic resonance imaging.

- integrity of the intracranial structures (see Chapter 5).
- Electroencephalography (EEG) records electric activity associated with forebrain structures (see Chapter 4). The EEG is rarely specific and in certain cerebral conditions it also lacks sensitivity. Although rarely, if ever, used as a diagnostic tool the EEG can provide confirmation of brain death (flat or isoelectric EEG). However, other factors such as patient body temperature, concurrent drug administration and cardiac function must be considered before brain death is diagnosed.

# Monitoring of animals with coma

Monitoring an animal that is comatose requires recognition, understanding and treatment of the secondary pathophysiological problem of intracranial disease (see Chapters 19 and 20). Life-threatening systemic complications should be recognized and treated. Neurological assessments should be frequently recorded to ensure recognition of trends in intracranial function. A coma scale is used as a guide to determining treatment and prognosis in humans with brain injury. A similar scale has been adapted for use in dogs (see Chapter 19); however, its role in determining treatment and prognosis is less clear. A common sense approach based upon diligent and repeated assessment of major neurological functions, such as level of consciousness and voluntary movement, is usually most important.

Animals are typically monitored in a critical care or intensive care area for signs of neurological deterioration. Parameters commonly monitored include heart rate and rhythm, respiratory rate and pattern, blood pressure, urine production, and pain. Neurological parameters monitored include pupil size and responsiveness to light, level of consciousness, behaviour and the ability to move and walk. Intravenous fluid therapy is given to maintain normal hydration and perfusion. Both dehydration and overhydration should be avoided. Monitoring of systemic blood pressure and central venous pressure may aid in re-establishing normovolaemia. Implanting a central venous catheter should be performed cautiously in an animal with increased ICP as manipulation or occlusion of the jugular vein for catheter placement may elevate ICP. Quick, efficient and atraumatic jugular catheterization is a must in this situation.

Routine systemic evaluations, such as a complete blood count (CBC), serum biochemistry, urinalysis, blood pressure, electrocardiography (ECG) and preand postprandial bile acids measurements are performed initially to determine overall systemic health. Radiographs of the thoracic and abdominal cavities are often helpful in quick assessment of these body cavities. If no obvious system abnormality is detected on routine screening tests, an advanced imaging study (CT or MRI) is indicated to determine whether an intracranial structural abnormality is the cause of the coma. If these studies are unavailable or not feasible, or if the clinical signs are mild, the animal should be

periodically monitored (hourly, if necessary) for deteriorating neurological function. If clinical signs are severe from the outset or worsen progressively, treatment for elevated ICP (e.g. fluid therapy to maintain normal blood pressure, mannitol) should be initiated.

# **Prognosis**

The prognosis of a comatose animal will ultimately depend upon the underlying cause. If the coma is the result of a disease process which is no longer progressing (e.g. head trauma) and if the secondary effects of intracranial disease can be recognized and controlled, the animal has a reasonable chance of recovery. In general, animals with lesions of supratentorial structures or the cerebellum have a better overall prognosis for recovery than those animals with lesions involving the brainstem (Colter, 1990). After the acute effects of brain disease are controlled (usually within 7 days) the goal is to allow time for brain healing and recovery of function to occur. Smaller animals are often better candidates for prolonged nursing care than are larger animals due to the ease of manipulation. Good nursing care (see also Chapter 24) includes the prevention of decubital ulcers in the recumbent animal and monitoring for secondary infections primarily of the pulmonary and urogenital systems. Recumbent animals should be placed on clean, soft bedding and turned frequently (at least every 4 hours). Physical therapy can begin as soon as possible if there are no unstable vertebral injuries. Physical therapy is individualized to the animal's needs but may include supported or non-supported walking, passive flexion and extension of the limbs, massage or swimming. Swimming may not be feasible with cats. A daily record of physical therapy will ensure that this is not overlooked, and allows several individuals, including the owner, to become involved in the healing process.

In general, clinical signs of unilateral supratentorial injury improve within the first 2 weeks following trauma. Usually the animal can walk by 4 weeks post-injury, although, residual paresis and blindness may continue. A tendency to circle may also persist, being especially prominent when the animal is distressed or excited. Recovery from brainstem injury may be less complete and residual signs commonly remain. Recovery from cerebellar injury often occurs in a similar time frame as for supratentorial injury. If the secondary effects of brain injury are controlled, many animals can recover from the primary brain insult associated with trauma.

# Specific neurological diseases

# Degenerative diseases

# Inherited neurodegenerative diseases

Clinical signs: The majority of degenerative diseases involving the nervous system result in clinical signs early in life, usually with an onset beginning at <1 year

of age. Many are breed related and presumed inherited (see Appendix 1 for a full list). Clinical signs are slowly progressive, with severe alterations in consciousness occurring relatively late in the disease course. Most cause multifocal neurological signs and cerebellar signs are often the predominant problem (see Chapter 12).

Pathogenesis: Neuronal degenerative diseases can affect any part of the nervous system and commonly result in dysfunction of the intracranial nervous system (Braund, 1987). Examples include: multisystem neuronal degeneration of Cocker Spaniels; spongiform degenerations in Labrador Retrievers, Samoyeds, Silkie Terriers, Dalmatians (cavitating leucodystrophy), mixed-breed dogs and Egyptian Mau kittens; and multisystemic chromatolytic neuronal degeneration in Cairn Terriers. The pathogenic mechanisms of many of these diseases have not been fully elucidated.

Storage diseases are due to an inborn error of metabolism and the absence of a vital enzyme necessary to break down an endogenous body substance (Braund, 1987, 1994; March, 1996) (see Chapter 12 and Appendix 1). These substances then accumulate within the neuron or other cells associated with the nervous system and eventually cause cellular dysfunction. The numerous storage diseases of small animals have been reviewed previously (March, 1996).

**Diagnosis:** Ante-mortem diagnosis requires biopsy of affected tissue. Determining the lysosomal enzyme activity of brain and other cells may be helpful but is not universally clinically available (see Appendix 1). In some storage diseases inclusions may be present in white blood cells or hepatocytes.

**Treatment and prognosis:** In general there is no treatment available for inherited neurodegenerative diseases, but bone marrow transplantation may help in the future for the treatment of lysosomal storage diseases. Thus, currently these are ultimately fatal disorders, although the rate of progression of signs varies widely between diseases and individuals.

# Canine cognitive dysfunction

Clinical signs: This is a loosely described syndrome affecting older dogs. Affected dogs show chronic progressive behavioural abnormalities such as loss of learned behaviour, failure to recognize their owners and disturbed sleep cycles (Ruehl et al., 1997).

**Pathogenesis:** This syndrome has been likened to the early stages of Alzheimer's disease in people. Diffuse β-amyloid plaques may develop in the temporoparietal and entorhinal cortex (Cotman *et al.*, 2002). The aetiology and clinical consequences of these pathological changes are unclear in dogs.

**Diagnosis:** The diagnosis is made by ruling out other causes of behavioural abnormalities. Due to the nonspecific clinical signs associated with this clinical syndrome, it is difficult to make a definitive diagnosis. An

extensive evaluation for other causes of intracranial signs in older dogs, such as brain tumours, metabolic disorders, vascular-based diseases and hypertension-associated intracranial disease, should be undertaken.

**Treatment and prognosis:** Diets rich in antioxidants have been useful in slowing age-related behavioural changes in experimental colonies of dogs (Cotman et al., 2002). The use of L-deprenyl has also been advocated (Ruehl et al., 1997). Coupled with the difficulty in arriving at a definitive ante-mortem diagnosis, and the fact that the natural course of the syndrome has yet to be described in the population of pet dogs, it is often difficult to determine objectively whether any treatment for this disorder is beneficial. Readers are referred to behavioural texts for further information.

# **Anomalous diseases**

Anomalous conditions, such as exencephaly (mass of skin-covered meninges and cerebral hemispheres that project through an opening in the cranial cavity), hydranencephaly (each cerebral hemisphere is reduced to a fluid-filled sac with the wall of the sac containing the leptomeninges, a glial membrane and ependyma), anencephaly (lack of a cerebral hemisphere) and other severe malformations of the intracranial structures, often result in early fetal or neonatal death (deLahunta, 1983). If animals survive birth, they may have significant alterations in consciousness and behavioural development.

#### Hydrocephalus

Hydrocephalus is the term used to describe a condition of abnormal dilation of the ventricular system within the cranium. Ventricular dilation occurs with some frequency in dogs and cats due to a variety of intracranial disease processes (Harrington *et al.*, 1996). Dog breeds predisposed to congenital hydrocephalus include the Chihuahua, Pomeranian, Yorkshire Terrier, English Bulldog, Lhasa Apso, Toy Poodle, Cairn Terrier, Boston Terrier, Pug, Pekingese and Maltese.

Clinical signs: Hydrocephalus can result in clinical signs due to loss of neurons or neuronal function, alterations in ICP and all of its consequences. Clinical signs of hydrocephalus reflect the anatomical level of disease involvement. Severity of clinical signs is not necessarily dependent upon the degree of ventricular dilation but rather on a host of concurrent abnormalities including the underlying disease process, associated ICP changes, intraventricular haemorrhage and the acuity of ventricular obstruction. In animals with severe hydrocephalus the compressed layer of cortex is prone to tearing, either spontaneously or with minor trauma, causing sudden onset of focal signs of forebrain disease.

 In young dogs, prior to ossification of the cranial sutures, hydrocephalus may contribute to abnormalities of skull development such as a thinning of the bone structure, a dome-shaped or bossed appearance to the head or a persistent fontanelle (Figure 8.7).

- A ventral and/or lateral strabismus has been noted in humans and animals with hydrocephalus. This may be referred to as the 'setting-sun sign' (Adams and Victor, 1989). Confusion remains as to the underlying reason for this clinical finding. It has been suggested that this appearance is associated with the skull deformity and distortion of the orbits. Others suggest that because this abnormality can be improved with shunting of the lateral and third ventricles, the strabismus is associated with pressure on the mesencephalic tegmentum (deLahunta, 1983).
- As a result of the involvement of supratentorial and brainstem structures in hydrocephalus, alterations in awareness and cognition are common. Many animals affected congenitally may appear to be less intelligent than normal and be difficult to house train. In addition to alterations in consciousness, circling, paresis and seizures may also be seen. Central visual dysfunction can occur with compression of the optic radiation and occipital cortex.
- Occasionally, when hydrocephalus is associated with fourth ventricle enlargement, there may be pronounced vestibular dysfunction.



8.7

7-week-old crossbreed puppy with pathologically confirmed hydrocephalus demonstrating a large domed skull.

**Pathogenesis:** Hydrocephalus can result from obstruction of the ventricular system (for example by a brain tumour), irritation of the ventricle (from inflammation or haemorrhage), increased size of the ventricles due to loss of brain parenchyma (hydrocephalus *ex vacuo*), be present without an obvious cause (congenital) or, rarely, be the result of overproduction of CSF associated with a choroid plexus tumour.

Ventricular obstruction can occur due to intraventricular or extraventricular obstruction (Figure 8.8). Hydrocephalus occurs in cats with CNS involvement in feline infectious peritonitis (FIP) as a result of ependymitis and vasculitis causing obstruction to CSF flow. Diffuse ventricular enlargement suggests congenital ventricular dilation or obstruction at the level of the lateral apertures or foramen magnum. Focal ventricular enlargement suggests focal obstruction or focal loss of brain parenchyma. It is not uncommon to have bilateral lateral ventricle enlargement that is asymmetrical. Animals with an asymmetrical appearance of



Non-contrast-enhanced transverse T1-weighted MR image of a dog with obstructive hydrocephalus due to a choroid plexus papilloma (CPP). The CPP is just visible in the left cerebellopontine angle. The fourth and lateral ventricles are dilated as a result of the tumour.

the ventricles should be critically evaluated for focal obstruction of, or impingement on, the ventricular system due to mass effect.

*Diagnosis:* The diagnosis of hydrocephalus is aided by information obtained from a variety of imaging and electrophysiological modalities. Historical, invasive techniques, such as pneumo- or contrast ventriculography, have been replaced by non-invasive evaluations, such as ultrasonography, CT and MRI (deLahunta, 1983).

Ultrasound examination can be used to diagnose hydrocephalus (Hudson et al., 1990; Spaulding and Sharp, 1990). This is most readily accomplished when a fontanelle is present providing an 'acoustic window' as ultrasound waves do not adequately penetrate the skull (see Chapter 5). Measurement of lateral ventricle size has been recorded in normal neonatal dogs and dogs with hydrocephalus. In general, correlation between the degree of ventricular enlargement and clinical signs is poor (Hudson et al., 1990). However, recently, ventricular enlargement (ventricle to brain (VB) ratio) was correlated to severity of clinical signs using transcranial Doppler ultrasonography in small breed dogs (Saito et al., 2003). Perhaps more importantly, asymptomatic dogs with a VB ratio of >60% all went on to develop neurological signs related to hydrocephalus and surgical shunting could be considered with these dogs (see below). The resistance index of the basilar artery, which directly correlates to ICP, can also be measured with transcranial Doppler ultrasonography; this index also correlates to neurological status in dogs with congenital hydrocephalus (Saito et al., 2003).

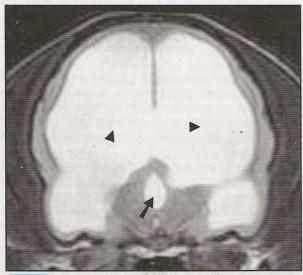
CT, as a non-invasive intracranial imaging modality, is often useful in defining ventricular size (Figure 8.9). As CSF is less attenuating than brain parenchyma (see Chapter 5), the ventricular system is usually readily identifiable on images due to its relative

blackness in comparison to parenchyma. CT evaluation also affords the ability to examine the majority of the ventricular system as well as additional intracranial structures. However, as stated previously, ventricular size alone does not always correlate with clinical signs and the clinical significance of the ventricular enlargement is difficult to predict.

MRI also affords evaluation of the ventricular system. This modality provides superior neural parenchyma resolution and is especially useful for evaluation of the infratentorial structures (Figure 8.10). It is now recognized that many toy breed dogs predisposed to hydrocephalus also have infratentorial anomalies, such as Chiari-like malformations, that potentially complicate their management and are detected only on MRI.



8.9 Transverse CT image of a dog with congenital hydrocephalus at the level of the midbrain. There is obvious dilation of the lateral ventricles. The mesencephalic aqueduct is visible (arrowed) and is not dilated.



T2-weighted transverse MR image of a dog with congenital hydrocephalus. The CSF appears white, highlighting marked dilation of the lateral (arrowheads) and third ventricles (arrowed).

Treatment and prognosis: Although the prognosis for animals with hydrocephalus is uncertain there are several medical and surgical treatment options, which may be beneficial. The choice of treatment is generally dictated by physical status, age of the animal and cause of the hydrocephalus. Medical treatment may include general supportive care and medications to limit CSF production and reduce intracranial pressure. Surgical treatment is designed to provide drainage of CSF from the brain to another site for absorption.

Medical management: Glucocorticoids are used to decrease CSF production, thereby, limiting ICP and further neurological injury (Harrington et al., 1996). Prednisolone at 0.25-0.5 mg/kg is given orally twice daily. The dose is gradually reduced at weekly intervals to 0.1 mg/kg every other day. This dose is continued for at least 1 month. Then the medication is discontinued if possible. Alternatively, dexamethasone may be given orally at 0.25 mg/kg every 6 to 8 hours. The dose can be gradually reduced over 2-4 weeks. Some animals can be adequately managed with long-term glucocorticoid administration at low doses. If no clinical benefits are observed within 2 weeks, or if side-effects develop other forms of therapy should be tried. Acetazolamide, a carbonic anhydrase inhibitor, is thought to reduce CSF pressure by decreasing CSF production. Its effectiveness in treating hydrocephalus is inconsistent, however. Mannitol, hypertonic saline and furosemide may be administered to provide temporary decreases in ICP and are reserved for emergency situations (see Chapter 19).

Surgical management: Surgery is generally required for those animals that do not improve within 2 weeks, if deterioration occurs during corticosteroid therapy or if there is an obstructive cause such as a tumour that cannot be resected.

As a successful outcome may be more likely in animals that have minimal clinical signs; surgery may be appropriate in animals with a VB ratio of >60%, although few owners are willing to undergo the expense and risk of shunt placement if their dog does not have neurological deficits.

The surgical procedures are designed to provide controlled CSF flow from the ventricles of the brain to either the peritoneal cavity or the right atrium of the heart. Shunt systems which have been designed for use in humans seem to work well for animals. The shunts have not been proven to be more effective than medical management but only surgical treatment offers the possibility of long-term control of the clinical signs.

Ventriculoperitoneal (VP) shunts are most commonly used in small animals (Figure 8.11). Complications of shunt placement occur in approximately 20% of cases and include excessive trauma to the cerebral parenchyma, migration of the shunt, infection and shunt blockage. Migration of the shunt is the most common of these complications and so special care should be taken when anchoring it to the skull (Personal communication, Galano 2004).





# 8.11

(a) Lateral and (b) ventrodorsal radiographs of a dog following ventriculoperitoneal shunt placement to treat congenital hydrocephalus. The shunt reservoir is visible in the cervical region (arrowed).

# Metabolic diseases

Numerous metabolic abnormalities may alter cerebrocortical and brainstem function (Cuddon, 1996). Liver disease (hepatic encephalopathy, HE), renal disease (renal encephalopathy), pancreatic disease (pancreatic encephalopathy) glucose abnormalities (hyper- or hypoglycaemia), electrolyte abnormalities (sodium, potassium, chloride, calcium, magnesium), cardiovascular diseases (resulting in ischaemia and hypoxia) and acid-base abnormalities are examples. Endocrine abnormalities, such as abnormalities of thyroid hormone and cortisol, may also affect consciousness (Joseph and Peterson 1992; Jaggy et al., 1994; Feldman and Nelson, 1996). The following discussion of metabolic encephalopathies addresses the basic diagnostic and treatment regimens for the underlying diseases but an in-depth description of these subjects is beyond the scope of this text; further details can be found in standard internal medicine texts.

# Hepatic encephalopathy

When liver function is compromised due to organ failure, hepatic microvascular dysplasia or portosystemic shunting, central nervous system signs quickly ensue.

Clinical signs: Animals with HE are most often admitted for seizures, ptyalism (especially in cats) and

changes in mental status, which range from behavioural abnormalities to coma. Signs of hepatic dysfunction such as weight loss, polydipsia, anorexia and vomiting may be present. These animals are often sensitive to administration of benzodiazepines and barbiturates as both drugs are metabolized by the liver. Overzealous administration of these types of drugs may result in stupor and coma due to CNS depression.

**Pathogenesis:** HE results when numerous putative neurotoxins reach the brain unmetabolized as they pass through an abnormally functioning liver (Cuddon, 1996). Suspected toxins include neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate, aromatic amino acids, mercaptans, ammonia and skatoles.

*Diagnosis:* The diagnosis of HE is supported by abnormal liver function studies. Other associated abnormalities may include: microcytic red blood cells; low albumin, cholesterol, glucose and urea concentrations; and elevated liver enzymes if there is parenchymal damage. The preferred methods for the imaging diagnosis of portosystemic shunts include mesenteric portography, abdominal ultrasonography and perrectal scintigraphy.

# Treatment and prognosis – Treatment of HE aims to:

- 1. Treat the underlying disease of the liver (see medical and surgical texts for descriptions related to different liver diseases)
- 2. Treat any associated seizures
- 3. Reduce the level of haematogenous neurotoxins, such as ammonia.

A diet of high quality, low quantity protein can help to minimize ammonia production in the gut. Lactulose (0.5-1.0 ml/kg orally q8h) is frequently used to assist with this aim as it reduces the amount of colonic ammonia production by changing bacterial flora and decreasing gastrointestinal transit time, and 'traps' ammonia by creating an acid environment within the gut. Lactulose can also be administered as an enema in comatose patients at a dose of 20 ml/kg g4-6h. Neomycin (20 mg/kg orally g8h), ampicillin (22 mg/kg orally q8h) or metronidazole (7.5 mg/kg orally q8h) can be given additionally to reduce urea-splitting bacteria in the colon. Potassium bromide may be the anticonvulsant of choice in these cases but would require 'load-dosing' to attain rapid steady-state levels (see Chapters 7 and 19). The prognosis depends on the underlying hepatic disease and the initial response to medical therapy.

# Hypoglycaemia

Clinical signs: Hypoglycaemia can cause a variety of neurological signs including anxiety, a ravenous appetite, lethargy or depression, tremors, seizures and coma. Exercise or fasting may precipitate signs. The speed with which the glucose concentration changes

influences signs to a certain extent. Sudden drops in blood glucose cause a sympathetic discharge, hence anxiety and hunger, whereas chronically low glucose levels cause lethargy. A peripheral neuropathy causing a stilted pelvic limb gait has been reported in dogs with insulinoma (Shahar *et al.*, 1985; Braund *et al.*, 1987; Bergman *et al.*, 1994; Schrauwen *et al.*, 1996) (see Chapter 14).

**Pathogenesis:** Decreases in blood glucose alter intracranial neuronal function (Howerton and Shell, 1992). Hypoglycaemia can occur secondary to insulinoma, liver disease, hypoadrenocorticism, glycogen storage diseases, insulin overdose (in diabetics) and extrapancreatic neoplasia. Toy breeds and neonates may become hypoglycaemic during times of stress.

Diagnosis: Serum glucose concentrations of <3 mmol/l (<60 mg/dl) accompanied by consistent neurological signs are suggestive of significant hypoglycaemia. If glucose concentrations decrease slowly, some animals can have lower concentrations (<2 mmol/l; <35 mg/dl) without serious clinical problems. Any single glucose concentration that is abnormally low should be rechecked to eliminate sample handling or laboratory error. If the glucose concentration is consistently low, further investigation of the underlying cause is indicated.

Treatment and prognosis: Treatment and prognosis ultimately depend on the underlying cause. Feeding multiple small meals can help dogs with insulinomas. Direct correction of hypoglycaemia is indicated in emergency situations. Syrup can be applied to the gums in situations when intravenous administration is not available (for example, by owners). (For further information on the intravenous administration of glucose see Chapter 19.) It should be noted that if the suspected diagnosis is insulinoma, giving large amounts of glucose, either in the form of a large meal or intravenously, can cause a further increase in insulin release into the circulation and exacerbate the problem.

Central blindness is a frequent finding in animals that present with hypoglycaemic seizures. This can be a permanent residual deficit if severe damage has occurred.

# **Electrolyte disturbances**

**Sodium abnormalities:** Both hypernatraemia and hyponatraemia may affect the CNS and result in abnormalities of mentation.

#### Hypernatraemia:

Clinical signs: Lethargy and irritability progress to ataxia, tremors, myoclonus, seizures, blindness, coma and death.

Pathogenesis: Hypernatraemia is most extreme in animals with abnormalities of thirst and drinking; this can be a direct consequence of hypothalamic disease (Bagley, 1994). Hypernatraemia is synonymous with hyperosmolality and can lead to shrinkage of brain parenchymal cells. This can cause stretching of small

intracranial blood vessels and haemorrhage. After 2–3 days, the brain attempts to compensate for the altered extracellular sodium levels by producing osmotically active intracellular substances (idiogenic osmoles). Thus, overly rapid correction of chronic hypernatraemia can cause sudden swelling of the brain parenchyma and ultimately be fatal.

Diagnosis: Demonstration of an abnormal electrolyte level in the presence of an encephalopathy that improves with appropriate correction confirms diagnosis. Imaging of the brain and CSF analysis should be performed if a hypothalamic lesion is suspected.

Treatment and prognosis: Guidelines for treating sodium abnormalities have been suggested but are crude. Appropriate therapy is based upon replacement of the water deficit (calculated using the following equation) in addition to addressing the underlying cause:

In any animal with established hypernatraemia, the water deficit should be corrected either orally or by fluid therapy administered conservatively over 2-3 days. An isotonic maintenance fluid, such as lactated Ringer's solution, should be used beginning at 1.5 times normal maintenance rate of administration. Serum sodium concentrations should be monitored frequently (i.e. every 4-6 h) and fluid therapy administration rates adjusted conservatively up or down depending upon the serum sodium level. Typically sodium concentrations are restored over 48-72 hours. If serum sodium concentrations are lowered too rapidly cerebral oedema may result with clinical deterioration in consciousness. Therapies such as mannitol (0.25-1.0 g/kg i.v.) are often necessary for treatment of these animals.

# Hyponatraemia:

Clinical signs: Lethargy, nausea and vomiting progressing to seizures, coma and death.

Pathogenesis: Hyponatraemia is synonymous with hypo-osmolality and can result in swelling of brain parenchymal cells with subsequent brain oedema. After 2–3 days the brain will try to compensate for this by actively extruding osmotically active intracellular components, and again over-rapid correction of sodium concentrations can be fatal.

Diagnosis: Demonstration of an abnormal electrolyte level in the presence of an encephalopathy that improves with appropriate correction confirms diagnosis. Imaging of the brain and CSF analysis may be indicated.

Treatment and prognosis: Too rapid correction of an established hyponatraemia can result in thalamic lesions thought to be similar to central pontine myelinolysis in humans (O'Brien et al., 1994). Sodium deficits are typically replaced using 0.9% saline. Appropriate therapy is based upon the following equation in addition to addressing the underlying cause:

Sodium deficit (mmol/l) = 0.6 x bodyweight (kg) x (normal sodium – patient's sodium)

**Potassium abnormalities:** Alterations in potassium tend to affect muscle function more so than CNS function (see Chapter 17). However, poor cerebral blood flow secondary to cardiac arrhythmias resulting from alterations in potassium may affect intracranial functions.

Calcium abnormalities: Hypercalcaemia may result in nervous system depression and hypocalcaemia can result in increased nervous system excitability manifested as seizures and tremors, as well as abnormal neurotransmission (see Chapters 7 and 12).

# **CNS** perfusion

Alterations in cerebral blood flow and perfusion, including ischaemia and hypoxia, can affect neuronal function. These alterations may occur from systemic hypoperfusion due to cardiac or pulmonary disease. Hyperviscosity from increases in blood cells (e.g. polycythaemia vera or leukaemia) may also result in intracranial disease. Anaemia or haemoglobin-related toxicity (i.e. cyanide toxicosis) that affects the oxygencarrying capacity of red blood cells can also affect oxygen delivery to the brain. Primary abnormalities of neuronal metabolic functions and energy metabolism may also result in abnormal cerebrocortical function.

#### Hypothyroid myxoedema coma

Clinical signs: This is an extremely rare presentation of hypothyroid dogs; Dobermann Pinschers seem to be over-represented. Affected animals become stuporous to comatose, severely hypothermic (with an absence of shivering) and bradycardic. More classic signs of hypothyroidism, such as weight gain, lethargy and dermatological abnormalities, are also present.

**Pathogenesis:** Myxoedema coma occurs in severely hypothyroid animals as a result of a hypometabolic state. The aetiology of coma is not understood but signs seem to be triggered by a stressful event.

**Diagnosis:** This is confirmed by measurement of thyroxine levels, which should be extremely low.

**Treatment and prognosis:** Thyroxine levels can be increased rapidly in emergency by intravenous administration of levothyroxine (Henik and Dixon, 2000). Unfortunately this disease carries a poor prognosis.

# **Neoplastic diseases**

Brain tumours primarily affect older dogs and cats. While some estimates exist on the frequency of brain tumours in dogs the actual incidence is not known. Brain tumours may arise primarily from brain or its surrounding tissues, may extend into the brain from adjacent structures or may metastasize to the brain from another location in the body. The increased reporting of brain tumours is no doubt the result of

increased diligence on the part of owners to pursue the causes of intracranial signs coupled with the increased availability and use of advanced imaging modalities such as CT or MR imaging for ante-mortem diagnosis of intracranial disease.

In a retrospective review of 97 dogs with brain tumours diagnosed at the author's hospital 95% of the affected dogs were 5 years or older at the time of diagnosis (Bagley *et al.*, 1999). The median age of dogs diagnosed with a brain tumour was 9 years (range 4–13 years). The most commonly affected breeds included Golden Retrievers, mixed breeds, Labrador Retrievers, Boxers, Collies, Dobermann Pinschers, Schnauzers and Airedales. A retrospective review of 160 cats with intracranial neoplasia found the median age at the time of diagnosis was 11.3 years (± 3.8 years) (Troxel *et al.*, 2003).

#### Clinical signs

The clinical signs relate to the location of the tumour or result from secondary effects of the tumour (e.g. raised ICP as a result of obstructive hydrocephalus causing coma). Most dogs (76%) with brain tumours in the author's hospital had lesions of the supratentorial space. The most common presenting complaint in these dogs was seizures. While seizures are often reported to be a clinical manifestation of brain tumour in dogs, the actual incidence of seizures associated with intracranial tumours is not well established. In a series of 21 dogs with brain tumours, eight had seizures. McGrath (1960) described the clinical features of 79 dogs with a brain tumour wherein 36 dogs (46%) had seizures. In another series of 43 dogs with rostral cerebral tumours, 22 (51%) had seizures (Foster et al., 1988). Seizures are sometimes the only sign of a structural intracranial abnormality when the remaining neurological examination findings are normal. This is especially true with more rostral and olfactory lobe lesions (Palmer et al., 1974; Foster et al., 1988). Therefore, seizures that begin in dogs >5 years of age regardless of associated neurological examination abnormalities should increase one's level of suspicion that a brain tumour may be present.

Most feline intracranial neoplasia (87.3%) affects the supratentorial space (Troxel *et al.*, 2003). The common neurological signs observed in these cats were: altered consciousness, such as depression, stupor or coma (26%); circling (22.5%); seizures (22.5%); ataxia (16.9%); and behavioural changes (15.6%).

# **Pathogenesis**

Tumours of the intracranial space may be primary (arise from tissues in the intracranial space) or secondary (arise from tissues adjacent to the intracranial space or from metastasis from far-removed tumours) (Bagley *et al.*, 1992; Moore *et al.*, 1996). Primary intracranial tumours include meningiomas, gliomas (including glioblastomas, astrocytomas and oligodendrogliomas), ependymomas and choroid plexus tumours. Pituitary tumours, while potentially arising from non-neural tissue, are sometimes included in this group.

Neoplasia secondarily involves the brain via metastasis or via direct extension from extraneural sites. Primary tumours within the skull, nasal cavity or frontal sinuses can extend directly into the brain (Smith et al., 1989; Moore et al., 1991). Often with caudal nasal cavity tumours signs of intracranial extension (e.g. seizures) occur prior to, or without, other signs of nasal disease. Numerous tumours of older animals metastasize to the brain including haemangiosarcoma, lymphosarcoma, and mammary gland and other carcinomas (Moore and Taylor, 1988; Waters et al., 1989; Fenner, 1990). The incidence of intracranial metastasis is often underestimated as the brain is not always examined during a routine necropsy; one study on feline intracranial neoplasia found that 5.6% of all tumours were the result of metastatic disease (Troxel et al., 2003). Tumours that readily metastasize to the lungs may be more likely to metastasize to the brain (Waters et al., 1989). The cortical grey/white junction is a common area of metastasis due to the increased vascularity, with brainstem and spinal cord metastasis less frequent. Choroid plexus tumours may metastasize through the CSF to other areas of the brain or spinal cord ('drop-mets') (Adams and Victor, 1989). In some instances, spinal signs from choroid plexus metastasis may be the first sign of the presence of the tumour. Diffuse intracranial tumours, such as carcinomatosis, are also possible.

Other tumours involving the brain are uncommon and include lymphosarcoma, germ cell tumours, dermoid and epidermoid cysts and craniopharyngiomas. Many of these tumours, surprisingly, are primarily seen in younger animals. Lymphoma made up 16% of all feline intracranial neoplasia reported in a recent report of 160 cases (Troxel *et al.*, 2003). Only 13% of these cases were focal masses with the others being diffuse diseases of the cerebrum or the brainstem, and approximately 70% of cases represented multicentric lymphoma.

*Meningiomas:* These are the most common brain tumours in dogs and cats (Bagley *et al.*, 1992; Troxel *et al.*, 2003). These tumours arise from the arachnoid layer of the meninges developing from the periphery of the brain parenchyma and expanding inward. Pre-

dominantly cystic meningiomas, often involving the olfactory area, have also been described (Bagley *et al.*, 1996). Meningiomas are usually histologically benign. However, in dogs, meningiomas tend to be more infiltrative to cortical parenchyma than in cats, where meningiomas are often well encapsulated.

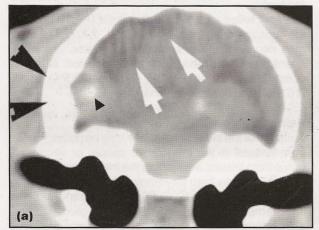
Gliomas: These arise from the supporting cells of the brain parenchyma. These include astrocytes and oligodendrocytes forming astrocytomas, oligodendrogliomas and the extremely malignant glioblastoma multiforme. Brachycephalic breeds of dogs such as Boxers and Boston Terriers may be more often affected with these tumours. Ependymal and choroid plexus tumours arise in or around the ventricular system. Choroid plexus tumours arise from areas where the choroid plexus is concentrated (i.e. the lateral, third and fourth ventricles) (Ribas et al., 1989). Because of their association with the ventricular system, associated hydrocephalus is common.

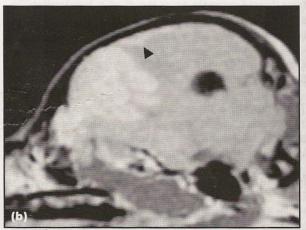
*Pituitary tumours:* Pituitary tumours may result in signs of endocrine diseases (e.g. hyperadrenocorticism, acromegaly) or signs primarily related to CNS dysfunction (Sarfaty *et al.*, 1988; Davidson *et al.*, 1991). Macroadenomas may enlarge dorsally from the sella and compress the diencephalon. Neurological impairment can be surprisingly minimal. The relative size of the tumour can not be predicted from endocrine test results (Kipperman *et al.*, 1992).

#### Diagnosis

Advanced imaging modalities such as CT or MRI are the most commonly used tests for patients with suspected neoplasia. Features of primary brain tumours have been reviewed (Turrel *et al.*, 1986; Gavin *et al.*, 1995; Tucker and Gavin, 1996).

**Meningiomas:** These most commonly appear as a broad-based, extra-axial (arising outside and pushing into the parenchyma) contrast-enhancing mass on CT or MR images (Figure 8.12). These tumours may

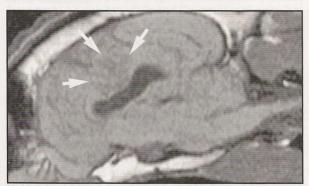




(a) Transverse contrast-enhanced CT image of the brain of a 14-year-old cat that presented with seizures. There is a small contrast-enhancing mass in the right temporal lobe with a mineralized centre (arrowhead). In addition, the overlying skull is thickened (hyperostosis; black arrows). Because the meningioma is lying in the subarachnoid space, the brain has been pushed away from the skull (white arrows) and there is an accumulation of CSF in the resultant space. (b) A sagittal contrast-enhanced T1-weighted MRI of an 8-year-old Bichon Frisé with a meningioma. There is a large contrast-enhancing mass with a broad base in contact with the surface of the brain and extending along the meninges (arrowhead) (dural tail sign).

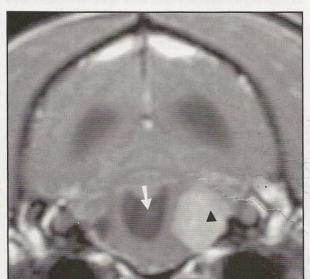
contain haemorrhage or be calcified, in addition to having large cystic areas. With CT, the two former components result in a hyperdense (more white) appearance on pre-contrast studies. Haemorrhage may have a varied appearance on MRI depending on the duration of the haemorrhage.

**Gliomas:** The CT and MR appearance of gliomas is varied, and enhancement after contrast administration is not consistently seen. A tumour confined within the parenchyma of the brain is characteristically seen. Gliomas are not always visible on CT images and so MR imaging is advised in older brachycephalic breeds of dog with focal forebrain signs (Figure 8.13).



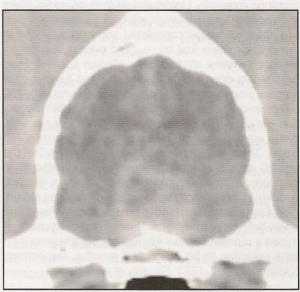
8.13 A sagittal contrast-enhanced T1-weighted MRI of a 9-year-old mixed-breed dog. The mass is an indistinct hypodense area lying in the parietal lobe (arrowed) and has not been enhanced with contrast. Histopathology confirmed it was a high grade glioma.

**Choroid plexus tumours:** Due to the concentration of blood vessels within the mass, choroid plexus tumours often become markedly enhanced after intravenous contrast medium administration (Figure 8.14). Obstruction of the ventricular system may result in hydrocephalus.



8.14 A transverse contrast-enhanced T1-weighted MRI at the level of the pons in a 7-year-old Border Collie. There is a large homogeneous contrast-enhanced mass in the left cerebellopontine angle (arrowhead) and the fourth ventricle is dilated (arrowed). Histopathology confirmed it was a choroid plexus papilloma.

**Pituitary tumours:** These may be found in the sella or suprasellar location. Smaller tumours are more readily seen with MR imaging especially with dynamic contrast studies. Macroadenomas may enlarge dorsally and invade or compress the diencephalon. Smaller tumours are more readily seen with MR than with CT imaging (Figure 8.15).



8.15 A contrast-enhanced transverse CT image of a 6-year-old Labrador Retriever that presented for unexplained pain and compulsive pacing. There is a large contrast-enhancing mass over the pituitary fossa. The mass has a cystic area and was confirmed at necropsy to be a pituitary adenocarcinoma.

CSF analysis is often not helpful for definitive diagnosis of a brain tumour and in some instances may be misleading. Classically, CSF in dogs with a brain tumour contains increased protein without a concurrent pleocytosis (albuminocytological dissociation). However, in a significant proportion of these dogs cellular changes consistent with inflammation are present and interpreted alone, may falsely suggest a primary inflammatory disease (encephalitis or meningitis) (Bailey and Higgins, 1986; Carrillo et al., 1986). Occasionally, CSF in a dog with a brain tumour will be normal. The presence of neoplastic cells in the CSF is specific; however, it is a very rare finding. This may occur more often with lymphoma, carcinomatosis and choroid plexus tumours. Median CSF total protein and nucleated cell count of 28 cats with variable types of intracranial neoplasia were 38.0 mg/dl (range 16-427 mg/dl; reference range <25 mg/dl) and 5 cells/µl (range 0-162 cells/μl; reference range <5 cells/μl), respectively (Troxel et al., 2003).

# **Treatment**

The treatment for brain tumours in dogs and cats depends upon tumour type, tumour location, history of the tumour, associated morbidity and/or mortality of the treatment modality and cost. While studies of the treatment of brain tumours in dogs and cats exist, many suffer from incomplete diagnoses, non-standardized treatment protocols, lack of a control population and differing tumours being grouped together to increase

overall study numbers. These problems make it difficult to give definitive statements about treatment efficacy in dogs with brain tumours.

Surgical removal: Surgical removal is ideal for superficially located, encapsulated, relatively small, benign tumours of which meningiomas would be the most common example. Unfortunately in dogs, even when meningiomas are histologically benign, these tumours are often not well encapsulated and hence difficult to remove surgically and micro-, and even macroscopic, disease remains after surgery. Median survival times reported in dogs with all types of brain tumour after surgery alone vary but tend to cluster around 140-150 days (Heidner et al., 1991; Niebauer et al., 1991; Jeffery and Brearley, 1993; Axlund et al., 2002). For meningiomas, median survival times may be slightly longer (240 days). There is a significant risk of mortality within the first 30 days of surgery for animals with infratentorial compared to those with supratentorial tumours. Surgical excision is more readily accomplished in cats as meningiomas in this species tend to be well encapsulated and easily delineated from normal brain. Studies have determined a median survival interval of cats after meningioma resection to be 22 and 27 months, respectively (Gallagher et al., 1993; Gordon et al., 1994).

Conventional radiation therapy: Conventional radiation therapy has been shown to be effective for brain tumours in dogs (Evans et al., 1993; LaRue and Gillette, 2001). Radiation therapy is more able to control tumour progression and, in some rare instances, it may eradicate the tumour completely. The main goal of the treatment is to administer to the tumour the highest possible dose of radiation while minimizing the dose to the surrounding normal tissue. Treatment protocols and survival analysis for radiation therapy of brain tumours have been reviewed. From these limited studies, median survival in dogs treated with conventional radiation therapy is approximately 150–350 days (see Chapter 23).

Chemotherapy: This is used as primary therapy or as an adjunct to surgery in selected instances for animals with brain tumours, typically in treatment of gliomas (Dimski and Cook, 1990; Fulton, 1991). BCNU (carmustine) or CCNU (lomustine) are alkylating agents that have some effectiveness primarily against gliomas. These are given intravenously or orally (CCNU) at 3–6 week-intervals (depending on the protocol). Side-effects include bone marrow suppression (at any time), liver disease and pulmonary fibrosis. Other chemotherapeutic agents that have been used for primary CNS lymphoma include cytosine arabinoside (crosses the blood–brain barrier readily) and methotrexate (see Chapter 22).

# **Prognosis**

Ultimately, the prognosis of an animal with a brain tumour will depend upon the adequacy of local tumour control. Currently, radiation therapy and surgery have provided the longest survival times in dogs with brain tumours, however, rarely is the median survival of these dogs over 1 year. In a minority of animals, survivals are far greater than 1 year, and these increased survival times should be used as a goal to achieve in greater numbers of cases. Cats appear to have an overall better prognosis than do dogs primarily because brain tumours in cats are often benign meningiomas, and are readily surgically removable. Surgical removal of brain tumours has a higher morbidity associated with treatment compared with radiation therapy. However, surgery also has the potential for cure and the decompression afforded can be life-saving in animals with severe deficits. Increased early recognition, through more widespread use of advanced intracranial studies, coupled with improvements in surgical and radiation therapies will hopefully provide an increased quantity and quality of life for animals with brain tumours.

# **Nutritional disorders**

# Thiamine deficiency

Thiamine deficiency (see Chapter 10) most commonly occurs in anorexic cats or cats that are fed all-fish diets containing thiaminase; however, it can also occur in dogs. This deficiency results in polioencephalomalacia of the oculomotor and vestibular nuclei, the caudal colliculus and the lateral geniculate body (deLahunta, 1983). Early non-specific signs are typically lethargy and inappetence. The earliest neurological sign is bilateral vestibular ataxia, which appears as an abnormal broad-based stance and loss of balance. If untreated, signs progress to semi-coma, persistent vocalization, opisthotonus and death. Diagnosis and treatment are discussed in Chapter 10.

# Infectious diseases

#### **Encephalitis and meningitis**

Encephalitis and meningitis (see Chapters 10, 13 and 15) often exist concurrently in dogs and cats. Numerous infectious agents (Figure 8.16) have been incriminated

Infectious agents	Examples			
Viral	Distemper, parvovirus, parainfluenza, herpes, feline infectious peritonitis, pseudorabies, rabies, feline leukaemia, feline immunodeficiency virus			
Bacterial	Escherichia coli, Streptococcus spp., Staphylococcuspp., Klebsiella spp.			
Rickettsial	Rocky Mountain spotted fever, Ehrlichia			
Spirochaetes	Lyme disease, leptospirosis			
Fungal	Blastomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, aspergillosis			
Protozoal	Toxoplasmosis, neosporosis			
Algal	Protothecosis			

Examples of infections that cause brain disease. (Data from Kornegay, 1978; Greene et al., 1985; Meric, 1986; Dow et al., 1988; Hass et al., 1989; Hoskins et al., 1991; Baroni and Heinold, 1995; Muñana, 1996).

(Meric, 1986; Muñana, 1996). These include both infectious and non-infectious aetiologies. Incidence of infectious agents causing meningitis varies with geographic location. Most meningitis syndromes (at least 60%) in small animals do not have a definable infectious cause.

Infectious agents causing brain disease are summarized in Figure 8.16. Non-infectious agents of the supratentorial structures include some specific diseases such as granulomatous meningoencephalitis (GME), breed-specific encephalitis and meningitis and many non-specific entities (Oliver *et al.*, 1997). Chapters 10, 13 and 15 have further details on the diagnosis, treatment and prognosis of inflammatory CNS diseases.

#### Parasitic disease

Parasites most commonly affect the forebrain during aberrant migration. Examples include *Toxocara*, heartworm and *Cuterebra* larvae (Meric, 1986). *Cuturebra* is one notable example that is speculated to be associated with intracranial disease in cats (Glass *et al.*, 1998). Treatment is directed at parasite removal. Anthelmintics are rarely effective when the CNS is involved. Anti-inflammatory drugs may be helpful.

# Idiopathic diseases

# Narcolepsy/cataplexy

Narcolepsy (excessive daytime sleepiness) and cataplexy (periods of acute muscular hypotonia) are episodic disorders that may mimic syncope and seizure (deLahunta, 1983). Further details can be found in Chapter 17.

#### Traumatic diseases

Traumatic injury remains a common cause of brain dysfunction in dogs and cats (Dewey et al., 1993). Trauma to the brain can occur from exogenous or endogenous disease. Exogenous injury occurs most commonly from automobile trauma, although gun shot wounds and falls may also be causes. All of these disease processes result in mechanical disruption of intracranial tissues (primary injury). This primary injury may initiate a number of secondary pathophysiological problems, such as metabolic alterations in neuronal or glial cells, impairment of vascular supply to normal tissue (ischaemia), impairment of cerebrovascular autoregulation, haemorrhage (intraparenchymal, intraventricular, extradural or subdural), irritation (seizure generation), obstruction of the ventricular system, oedema formation, production of physiologically active products and increased ICP (Bagley, 1996a). (See Chapter 19 for a full discussion on the management of head trauma.)

# Toxic diseases

Numerous toxins can affect the nervous system either primarily or secondarily (Dorman, 1993; Dorman and Fikes, 1993). Examples of primary toxins include organophosphates, metaldehyde, lead, bromethalin and hexachlorophene. (See Chapter 12 for further details on clinical signs and treatment.)

# Lead toxicity

Lead toxicity usually results from ingestion of products containing lead. Removal of lead-containing paint via sanding may produce lead-laden dust. If this dust contaminates the fur of cats, toxic levels of lead may be ingested during normal grooming.

Clinical signs: Gastrointestinal signs and haematological abnormalities may accompany CNS signs. Nervous system signs include depression, seizures, ataxia, blindness and weight loss.

**Pathogenesis:** Lead inhibits the sulphydryl groups of enzymes that are important in metabolism.

**Diagnosis:** The diagnosis is best supported by recording increased lead levels in the animal's blood.

**Treatment and prognosis:** Chelation therapy with calcium EDTA or penicillamine may be necessary to improve clinical signs and treatment is usually successful.

#### Ivermectin administration

Ivermectin administration has been associated with intracranial signs and seizures in dogs.

Clinical signs: The signs reported in mildly affected animals include salivation, vomiting, tremors, mydriasis, bradycardia, confusion and ataxia. More severely affected animals may have seizures and become comatose, requiring mechanical ventilation. Clinical signs can deteriorate for up to 6 days after subcutaneous administration of ivermectin and take 3 weeks to resolve (Hopper et al., 2002). Collies and similar breeds are particularly susceptible to the toxic effects of ivermectin, most likely due to abnormalities in the cellular transport mechanisms (P-glycoprotein abnormalities as a result of mutations in the multiple drug resistance (MDR1) gene) (Mealey et al., 2001). Such breeds can therefore develop side-effects when administered doses as low as 100 µg/kg (normal dose range is 50-300 μg/kg).

**Pathogenesis:** Ivermectin is believed to be a GABA agonist that binds to the postsynaptic GABA receptor. Penetration of the CNS is poor in mammals unless administered at high doses or administered to animals with mutation in the *MDR1* gene.

Treatment and prognosis: Treatment centres on provision of adequate supportive care, which can mean prolonged mechanical ventilation in severely affected dogs. Additional drug therapy is controversial; temporary (30–90 minutes) reversal of coma can sometimes be achieved by administration of physostigmine. Picrotoxin, a GABA antagonist, has also been used in one dog to reverse coma and did improve the level of consciousness but caused seizures. Some dogs develop severe tremors and both diazepam and phenobarbital have been used to treat this problem. However, as both drugs act at the GABA receptor there are concerns that this worsens the level of consciousness.

In general, if adequate supportive care can be provided the prognosis is good.

# Vascular diseases

Vascular disease involving the forebrain is uncommon in animals in comparison with human beings (Thomas, 1996). However, feline ischaemic encephalopathy is a well recognized entity, and canine cerebrovascular accidents are more commonly recognized with the increased use of MRI.

# Clinical signs

The clinical signs reflect a forebrain abnormality and are usually acute in onset. Signs may be initially progressive as the vascular event results in secondary brain disease and oedema.

#### **Pathogenesis**

Thrombosis, infarction and haemorrhage can occur spontaneously, secondary to drug therapy (L-asparaginase, anticoagulants), with thrombocytopenia and other bleeding disorders, with trauma, hypertension and atherosclerosis from hypothyroidism, and with infection (septic emboli) (Bagley, 2000).

Feline ischaemic encephalopathy is an ischaemic necrosis of the cerebral hemisphere of cats (deLahunta, 1983). The distribution of the infarction is usually in the area supplied by the middle cerebral artery. Vascular lesions, however, are infrequently found at necropsy. The cause is unknown although there is speculation that it may be related to migration of Cuterebra larvae (Glass et al., 1998).

# Diagnosis

Haemorrhage and infarction may be seen with CT and MRI. CSF analysis often contains mild elevations in protein. Identification of any underlying disorders is important.

#### Treatment and prognosis

Treatment is aimed at the underlying cause, e.g. treatment of hypertension or Cuterebra. However, in animals with severe signs appropriate supportive care and management of ICP is needed (see Chapter 19). Prognosis is good after the first 48 hours in nonprogressive disorders, such as feline ischaemic encephalopathy. Neurological deficits may persist.

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# Chapter 8 Coma, stupor and behavioural change

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# Disorders of eyes and vision

# **Jacques Penderis**

# Introduction

The neuro-ophthalmological examination combines aspects of the neurological examination with components of the ophthalmic assessment and is an important element of both disciplines. Armed with a basic knowledge of the visual pathways and pupillary light reflex, performing the neuro-ophthalmological examination is simple, quick and requires no expensive or specialized equipment. From a neurological viewpoint, the visual system is both fascinating and unique, in that the retina

and optic disc are the only components of the nervous system directly visible in the normal patient. Even in the absence of overt neuro-ophthalmological abnormalities, a thorough evaluation of the eyes, including a fundic examination, should always be performed in the neurological patient, as the underlying cause of neurological disease may be evident (Figure 9.1). Conversely, a full neurological examination should be performed in any animal with neuro-ophthalmological abnormalities.

Terms that are commonly used in clinical neuroophthalmology are defined in Figure 9.2.





Evaluation of the eyes should be performed even where neuro-ophthalmological abnormalities are not suspected. The iris thickening (a) and corneal precipitates (a,b) evident in this cat with central vestibular disease are suggestive of infectious agents (e.g. FeLV, FIV or *Toxoplasma*) or lymphoma as the cause of the neurological deficits. CSF analysis confirmed the presence of lymphoma. (© Comparative Ophthalmology Unit, Animal Health Trust.)

Term	<b>Definition</b>			
Anisocoria	Pupils of unequal or asymmetrical size			
Blepharospasm	Spasm of the orbicularis oculi muscle			
Consensual PLR	Application of a light stimulus to one eye causing reflex constriction of the opposite pupil			
Enophthalmos	Abnormal displacement or sinking of the eyeball into the orbit			
Esotropia	Convergent strabismus: deviation of the visual axis of one or both eyes towards that of the opposite eye. Also calle cross-eye			
Exophthalmos	Abnormal displacement or protrusion of the eyeball out of the orbit			
Exotropia	Divergent strabismus: deviation of the visual axis of one or both eyes away from that of the opposite eye. Also ca wall eye			
Miosis	Abnormal or excessive constriction of the pupil			
Miotic	Drug or agent that causes pupillary constriction			

Definitions of terms commonly used in clinical neuro-ophthalmology. (continues)

Term	Definition			
Mydriasis	Abnormal or excessive dilation of the pupil			
Mydriatic	Drug or agent that causes pupillary dilation			
Nystagmus	Rhythmical, involuntary movements of the eyeball with either fast and slow phases (jerk nystagmus) or, less commonly equal oscillations (pendular nystagmus)			
Ophthalmoplegia	aralysis of the eye muscles			
Ophthalmoplegia interna	Paralysis of the iris and ciliary muscles			
Ophthalmoplegia externa	Paralysis of the extraocular muscles			
Pan-ophthalmoplegia	Paralysis of the iris, ciliary muscles and extraocular muscles. Also called total ophthalmoplegia			
PLR	Pupillary light reflex. Also called the photomotor reflex			
Ptosis	Abnormal or paralytic drooping of the upper eyelid			
Strabismus	Abnormal deviation of the visual axis of the eye that the animal cannot overcome			
Xeromycteria	Abnormal dryness of the nasal mucous membrane and planum			

(continued) Definitions of terms commonly used in clinical neuro-ophthalmology.

# **Neuro-ophthalmological assessment**

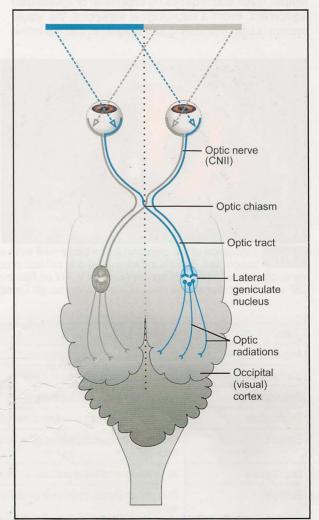
Before performing a detailed neuro-ophthalmological examination, it is essential first to observe the animal from a distance – the so-called 'hands-off' examination. This allows assessment of the patient's interaction with its surroundings, giving an indication as to the level of consciousness, as well as allowing for evaluation of any localizing signs (e.g. circling, hypermetria or head tilt). Identifying animals with decreased levels of consciousness is important, as these animals may respond inappropriately to tests requiring conscious input, without there actually being a lesion within the pathway being tested.

#### Vision

Vision is supplied by cranial nerve (CN) II (optic). The optic nerve supplies conscious perception of vision as well as visual input into unconscious reflex pathways, including the pupillary light reflex (also termed the photomotor reflex) and dazzle reflex. The visual pathways are demonstrated in Figure 9.3. As part of the 'hands-off' assessment, vision should be appraised by observing the animal interacting with and negotiating a strange environment (usually the consulting room) and navigating an obstacle course, and by performing the tracking response (evaluating whether the patient is able visually to follow moving but silent objects, such as a dropped piece of cotton wool).

The 'hands-on' assessment of vision includes the following.

 Visual placing response. The patient is held under its chest and brought up towards a table edge, but without letting the thoracic limbs touch the table. The normal patient should see the table and attempt to place its thoracic limbs on the surface of the table

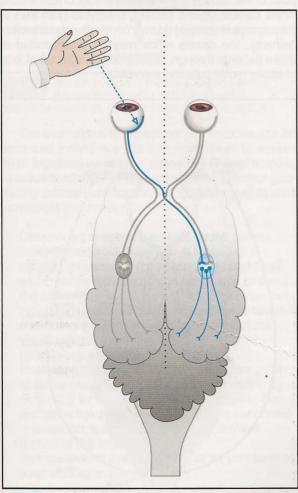


The visual pathways, demonstrating how each side of the visual field is represented within the opposite occipital (visual) cortex. As the degree of binocular vision in different species decreases, so a greater proportion of optic nerve fibres decussate at the optic chiasm. (Modified from Penderis, 2002.)

(Figure 9.4). This test therefore assesses vision, appropriate mentation and the postural control of the forelimbs, and is particularly useful in smaller patients.

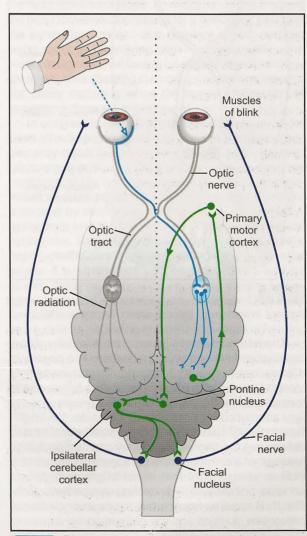


The visual placing response is a useful test to assess vision in smaller animals. If vision is intact, the animal should see the table edge and attempt to place both thoracic limbs on the surface. © Jacques Penderis.



The menace response is performed by making a threatening movement towards each eye in turn. Usually the visual stimulus is only directed at the nasal retina and not the temporal (lateral) retina and therefore only assesses the contralateral visual cortex as above. (Modified from Penderis, 2002.)

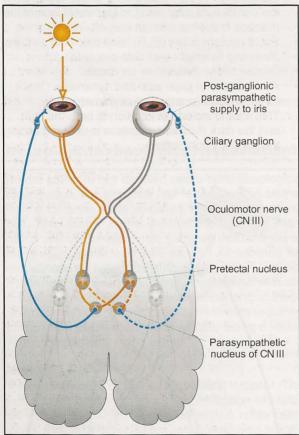
- Menace response. This learned response may not be present in normal animals under 12 weeks of age. The test is performed by making a threatening movement towards each eye in turn while closing the other eye, without touching the patient (Figure 9.5; see also Chapter 1). The normal response is for the patient to blink, with or without aversion of the head. The motor innervation of the muscles responsible for the blink is via the facial nerve and this test therefore also assesses the integrity of the facial nerve (CN VII) and cortical awareness (Figure 9.6). Furthermore, as the menace response is coordinated in the cerebellum, diffuse lesions of the cerebellum may result in ipsilateral loss of the menace response without loss of vision.
- Pupillary light reflex (PLR). See below for details.
- · Swinging flashlight test. See below for details.
- · Dazzle reflex. See below for details.
- Assessment of pupil size and symmetry. Check for anisocoria (unequal or asymmetrical pupils). This should include evaluation in both the light and the dark (further evaluation is detailed under the pupillary light reflex).



9.6 The menace response pathway. A lesion interrupting any part of the pathway may result in a menace deficit. (Modified from Penderis, 2002.)

# Pupillary light reflex

The PLR is supplied by CN II (optic) and the para-sympathetic portion of CN III (oculomotor). It evaluates the afferent visual pathways from the retina to just prior to the lateral geniculate nuclei in the thalamus (as detailed in Figure 9.7), while the efferent outflow is mediated via the parasympathetic portion of the oculomotor nerve (CN III). The PLR is tested by shining a bright light into the pupil and assessing for constriction of the pupil (direct reflex). The opposite pupil should constrict at the same time (consensual reflex) but it is not necessary to assess the consensual reflex if the direct PLR is intact in both eyes.



9.7 The pathway of the pupillary light reflex (divergence of the conscious visual pathway is detailed in light grey). (Modified from Penderis, 2002.)

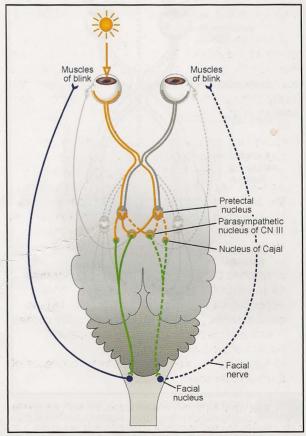
The normal direct PLR response is initial pupillary constriction followed by slight dilation. The degree of dilation increases with decreasing brightness of light stimulation and with longer stimulation times; this is termed pupillary escape and is the consequence of light adaptation of photoreceptors. Besides the brightness of the light used, the resting sympathetic tone also determines the degree of pupillary constriction, which means that a common cause of apparent failure of the PLR is using a light that is not bright enough in a nervous animal with high resting sympathetic tone. The PLR requires fewer intact axons than conscious perception of vision and therefore in partial lesions of the proximal visual pathways the situation may exist where there is loss of vision but the PLR is spared (Ferreira and Peterson-Jones, 2002).

# Swinging flashlight test

The swinging flashlight test, a variation of the PLR, allows evaluation of both the direct and consensual PLRs. The test is performed by 'swinging' the light stimulus from one eye to the other. If both the direct and consensual PLRs are intact, as the light stimulus is swung from one eye to the other each pupil can be seen to be already constricted as the light stimulus is directed at it (consensual response) and continue to remain constricted for the duration of the direct stimulus (direct response). Because the pupil that is being directly stimulated tends to constrict to a slightly greater extent than the contralateral pupil, slight further constriction may be evident as the light stimulus is directed at each eye.

### Dazzle reflex

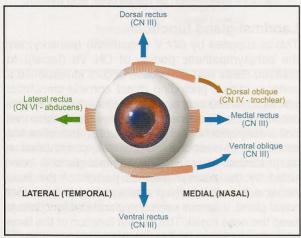
The dazzle reflex (Figure 9.8), supplied by CN II (optic) and CN VII (facial), is similar to the PLR in that it does not evaluate the cortical aspects of the visual pathway. In contrast to the PLR, in which the efferent arm is mediated by the oculomotor nerve, in the dazzle reflex the efferent pathway is mediated via the facial nerve. The reflex is induced by flashing a very bright light into the eyes with the normal response being a rapid blink. Loss of the dazzle reflex implies a subcortical lesion. While cortical lesions causing blindness (with loss of the menace response) do not interrupt the dazzle reflex pathway, the dazzle reflex may be exaggerated in these patients through disinhibition as a result of loss of upper motor neuron innervation.



9.8 The postulated pathway of the dazzle reflex – a subcortical reflex blink associated with a bright light stimulus. © Jacques Penderis.

# Extraocular muscular control of eyeball position and movement

The parasympathetic portion of the oculomotor nerve supplies the iris muscle for the PLR as well as the ciliary muscle (see Figure 9.7). The oculomotor nerve (CN III) also supplies motor innervation to the extraocular muscles (including the dorsal, medial and ventral rectus muscles and the ventral oblique muscle of the eyeball) and the levator palpebra muscle of the upper eyelid. The trochlear nerve (CN IV) innervates the dorsal oblique muscle. The abducent nerve (CN VI) innervates the lateral rectus and retractor bulbi muscles. The innervation to the extraocular muscles is detailed in Figure 9.9.



9.9 The innervation of the extraocular muscles (beside the retractor bulbi and levator palpebrae muscles). (Modified from Penderis, 2003a.)

The innervation to the extraocular muscles can be assessed individually but it is more usual to assess them together, as in most cases CN III is affected in isolation or all three nerves are affected together (producing external ophthalmoplegia). Assessing eyeball movement is achieved by:

- Observing the eye movements as the patient looks around voluntarily and in response to induced movements (by holding the head fixed and creating a distraction on either side to see if the animal can appropriately fix the gaze on the visual stimulus in a bilaterally coordinated fashion)
- Assessing the eyes for any asymmetry of the visual axis between the left and right eyes (strabismus or squint)
- Evaluating the innervation to the retractor bulbin muscles (innervated by the abducent nerve) by observing for retraction of the globe during the corneal reflex (stimulated by touching the corneal sensation is mediated via the ophthalmic branch of the trigeminal nerve)
- Retropulsion of eyeball to assess for presence of a retrobulbar mass.

The normal eye movements can be further evaluated by inducing physiological nystagmus (vestibulo-ocular reflex, which also evaluates CN VIII). The evaluation of physiological nystagmus is detailed below under vestibular control of eyeball position and

movement. The absence of normal physiological nystagmus indicates a vestibular lesion, a lesion affecting the extraocular muscles or their innervation or a lesion affecting the connection between the two.

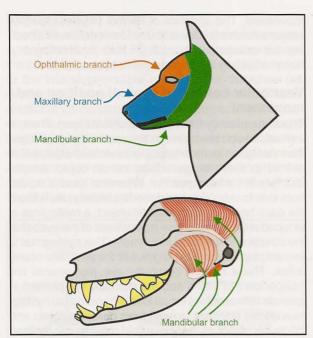
# Vestibular control of eyeball position and movement

This is supplied by CN VIII (vestibulocochlear). There is a close association between the vestibular system and the innervation to the extraocular muscles that allows an animal to keep its gaze fixed on an object despite changes in the head position. When the head is moved from side to side or up and down at a steady rate without the gaze being fixed on a single object, a nystagmus is induced with the fast phase movements of the eyeball in the direction of the head movement. This nystagmus is termed physiological nystagmus or the vestibulo-ocular reflex. These normal vestibular eye movements are independent of vision and are normally still present in animals with acquired visual loss. Physiological nystagmus allows the gaze to jump from object to object and follow the object as the visual field moves past, instead of the visual input recording a constant blur of passing information. Physiological nystagmus should stop once the head movement stops. An exception to this is where the head movement continues for a prolonged period in the same direction and at a constant speed, such as being spun on a revolving chair - in this situation the vestibular system has time to adapt, with the physiological nystagmus stopping during the constant movement but briefly restarting when the speed or direction of movement changes or is stopped.

In contrast to normal physiological nystagmus, lesions affecting vestibular input to the extraocular muscles may result in a static alteration in gaze direction (strabismus or squint) or involuntary eye movements (nystagmus) (as described later). The vestibular control of eyeball position and movement is therefore assessed by evaluating for strabismus, spontaneous nystagmus and the presence of normal physiological nystagmus. This should include elevating the animal's head (with the ears level) and holding it briefly elevated to see if a strabismus can be induced, as well as altering the animal's position (including turning it on its back) to assess for positional nystagmus. Other features of vestibular disease and associated cranial nerve deficits, including concurrent ipsilateral hearing deficits, facial nerve paresis, Horner's syndrome and trigeminal nerve lesions, may be present (see Chapters 10 and 11). In central (brainstem) lesions, the ascending proprioceptive and descending motor tracts to the limbs or the cerebellum may be affected.

# Somato-sensory innervation of the eyeball and eyelid

The three branches of CN V (trigeminal) – maxillary, mandibular and ophthalmic—are responsible for sensory information from the entire face (Figure 9.10), while the mandibular branch provides motor innervation to the masticatory muscles (masseter, temporal, pterygoids, rostral digastricus and mylohyoid). In addition, the ophthalmic and maxillary branches supply sensory information from the nasal mucosa.



9.10 The sensory innervation fields of the three branches of the trigeminal nerve. In addition, the mandibular branch provides motor innervation to the muscles of mastication. (Reproduced from *In Practice*; © Jacques Penderis)

The ophthalmic branch of the trigeminal nerve is assessed by performing the palpebral and corneal reflexes. The palpebral reflex is evaluated by touching the medial canthus of the eye and observing for the presence of a blink (mediated by CN VII, the facial nerve); the response to touching the lateral canthus is variable and probably innervated by the maxillary branch. The corneal reflex is evaluated by holding the eyelids open and lightly touching the cornea with a finger or cotton swab. The normal response to the corneal reflex is to retract the globe (mediated by CN VI, the abducent nerve) and prolapse the third eyelid. A more objective assessment of corneal sensation can be obtained by using a Cochet-Bonnet aesthesiometer (Brooks et al., 2000), but differences exist between breeds (with canine dolichocephalic breeds being more sensitive than brachycephalic breeds) and regions of the cornea (the centre being the most sensitive) (Barret et al., 1991). The Cochet-Bonnet aesthesiometer consists of a retractable nylon filament that can be varied in length from 0 to 6 cm. The nylon filament is touched against the cornea to determine the minimum length at which no conscious response is present and this gives a measure of corneal sensation. The force exerted by the nylon filament when it touches the cornea is inversely proportional to its length (the longer the filament, the less rigid it is). Other non-contact corneal aesthesiometers are available, including gas puff devices.

# Motor control of the eyelids

The motor innervation to the blink is supplied by CN VII, the facial nerve, which additionally innervates the other muscles of facial expression, supplies parasympathetic innervation to (among other structures) the lacrimal gland and lateral nasal gland and sensation to the

rostral two-thirds of the tongue and inner surface of the pinna. The parasympathetic innervation to the lacrimal gland splits from the facial nerve in the facial canal just prior to the close approximation between the facial nerve and the tympanic bulla.

Normal function of the facial nerve innervation to the orbicularis oculi muscles controlling the blink is assessed by:

- · Observing the animal for normal blinking
- The menace response (described in the vision section)
- The palpebral reflex (see above, under somatosensory innervation of the eyeball and eyelid).

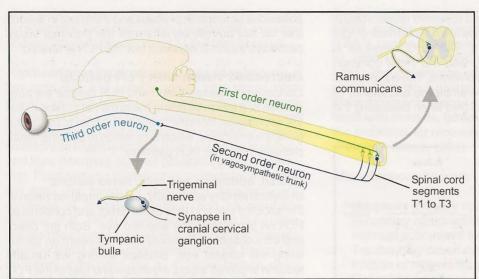
# Lacrimal gland function

This is supplied by CN V (trigeminal) (sensory) and the parasympathetic portion of CN VII (facial). Increased reflex tear production occurs in response to sensory stimuli (including direct corneal stimulation and exposure to cold and irritants) via the ophthalmic branch of the trigeminal nerve. Trigeminal lesions will not usually affect basal tear production but reflex tear production in response to corneal, conjunctival or nasal stimulation is lost. The lacrimal gland is innervated by the parasympathetic portion of the facial nerve, a branch of which also innervates the lateral nasal gland, a serous secreting gland that functions to keep the nose moist. The normal function of the facial nerve innervation to the lacrimal gland is assessed by performing a Schirmer tear test and examining the ipsilateral nostril for dryness.

# Sympathetic innervation to the eye and face

The sympathetic innervation to the head and eye is detailed in Figure 9.11. The pathway consists of first, second and third order neurons, with the first order neurons originating in the hypothalamus and rostral mid-brain and travelling down the tectotegmental spinal tract. The synapses with the second order neurons occur in the lateral horn of the spinal cord grey matter at the level of T1 to T3 spinal cord segments. The second order axons then leave the spinal cord with the T1 to T3 nerve roots. The brachial plexus innervating the thoracic limb is made up of contributions from nerve roots C6 to T1 (and sometimes T2) (see Chapter 16); part of the sympathetic supply leaving the spinal cord is therefore closely associated with the innervation to the thoracic limb.

The sympathetic axons separate from the T1 to T3 nerve roots as the ramus communicans and form the thoracic sympathetic trunk. The sympathetic trunk courses cranially in close apposition to the descending vagus nerve, together forming the vagosympathetic trunk within the carotid sheath. The sympathetic axons course rostrally through the caudal cervical ganglion, synapsing in the cranial cervical ganglion, adjacent to the tympanic bulla. From here the third order sympathetic axons pass through the middle ear and enter the cranial cavity with the glossopharyngeal nerve, then pass close to the cavernous sinus with the carotid artery, before leaving the cranial cavity via the orbital fissure in close approximation to the ophthalmic branch



9.11 The pathway of the sympathetic innervation to the eye and adjacent structures of the head. (Modified from Penderis, 2002.)

of the trigeminal nerve. The sympathetic supply to the eye and face innervates smooth muscle in the iris (dilator muscle), orbit, upper and lower eyelids (Müller's muscle), third eyelid and walls of blood vessels of the head. The effect is to contribute to the control of pupil and palpebral fissure size and maintain smooth muscle tone within the orbit (affecting eyeball position and third eyelid protrusion).

# Pharmacological evaluation of pupil function

Pharmacological testing may be useful in ascertaining the site of lesions affecting the efferent arm of the pupillary light reflex and the sympathetic supply to the eye (Horner's syndrome). However, pharmacological testing is not an exact science and the times to a response should be used only as a guide to the site of the lesion. There are differences in opinion on the utility of this form of testing and, in particular, on the concentrations of drugs used. Pharmacological testing should always be performed on both eyes, using the normal eye as a comparison, and it is important to apply the same dose of a drug to each eye. The basis of the tests lies in the development of denervation hypersensitivity (Rosenblueth and Cannon, 1936). Pharmacological testing of the sympathetic nervous system is discussed in more detail under Horner's syndrome in disorders of pupil size and function. Lesions affecting the efferent arm of the PLR (parasympathetic lesions producing mydriasis) can be localized further by application of direct and indirect parasympathomimetics.

• Differentiation between pre- and post-ganglionic lesions (ciliary ganglion) can be achieved by the topical administration of an indirect-acting parasympathomimetic (0.5% physostigmine drops). This drug inhibits cholinesterase, thereby increasing the concentration of acetylcholine at the neuromuscular junction. If the post-ganglionic neuron is preserved, it apparently releases low levels of acetylcholine continuously, the local concentration of which is increased by application of physostigmine. Iris constriction occurs 40–60 minutes before the control eye in

pre-ganglionic lesions, due to denervation hypersensitivity. However, in post-ganglionic lesions, physostigmine has no effect. If neither pupil responds, the test is considered a false negative and must be repeated.

The use of a direct-acting parasympathomimetic (1% pilocarpine drops) may allow differentiation between pre- and post-ganglionic lesions. Iris constriction occurs more rapidly in the affected eve than in the contralateral normal eve in postganglionic lesions, due to denervation hypersensitivity. Many people believe that concentrations of pilocarpine of 1% or greater will produce iris constriction, no matter what the neurological status, and therefore recommend the use of 0.05-0.1% pilocarpine (dilute the solution with saline) for differential detection of denervation hypersensitivity in post-ganglionic lesions. In practice this test is often non-specific, with a more rapid response indicating only that the lesion is neurological, rather than specifying the site. For example, this test can be used to differentiate mydriasis due to iris disease or pharmacological blockade from atropine or atropine-like substances, both of which are unresponsive to pilocarpine, from neurological disease (Scagliotti, 2000).

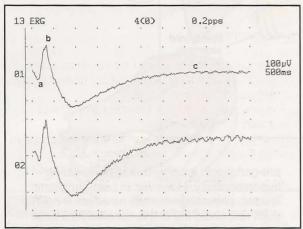
# Electrophysiological evaluation of the visual system

Electrophysiological evaluation of the visual system largely comprises electroretinography (ERG) and the less commonly performed visual evoked response (VER, also termed visual evoked potential).

# Electroretinography

The ERG is a test of retinal function, assessing both the rod and cone photoreceptors. It is useful for the identification of those cases of blindness due to retinal disease where the retina appears normal on ophthalmic examination (e.g. sudden acquired retinal degeneration). The ERG can be performed under general anaesthesia, or under sedation in a cooperative patient. A corneal

contact-lens electrode is used to record retinal voltage changes that occur in response to a defined flash of light or repeated flashes of light. The ERG response is expressed as a waveform, with the most common recording type having a- and b-waves. The waveform of the ERG and in particular the amplitude and latency of the a- and b-waves are measured when evaluating the ERG (Figure 9.12)



9.12 A typical normal electroretinogram from the right and left eyes of an adult dog. There are one negative (a) and two positive (b,c,) peaks. The a-wave is unquestionably caused by photoreceptor potentials. The origin of the b-wave is generally accepted to be Müller cells. The c-wave has been defined as the positive potential after the b-wave, and only occurs in approximately one third of adult dogs.

## Visual evoked potentials

Visual evoked potentials (VEPs) are the recordings of occipital cortex potentials, arising in response to brief flashes of light, using scalp recording electrodes and signal averaging techniques. The VEP waveform assesses the function of the central retinal region and post-retinal structures, including the optic nerve, optic tracts and visual cortex. The VEP is largely a research procedure and its use in clinical neuro-ophthalmology is limited.

# **Diseases**

To simplify the approach to the neuro-ophthalmology patient, the presenting clinical signs can be subdivided into a number of categories, with the most clinically significant being those where vision and/or the PLR are impaired:

- · Decreased vision with PLR deficits
- · Decreased vision with no PLR deficits
- Disorders of pupil size and function
- Disorders of eyeball position and movement
- · Disorders of blink
- · Disorders of the third eyelid
- Disorders of lacrimation.

As discussed previously, an occasional consideration is that the PLR requires fewer intact axons than

conscious perception of vision and therefore in lesions that do not completely interrupt the proximal visual pathways vision is impaired but the PLR is spared.

## Decreased vision with PLR deficits

Concurrent impaired vision and PLR deficits are suggestive of a lesion affecting the proximal portion of the visual pathway, from the retina to just prior to the lateral geniculate nucleus, which is common to both the visual pathways and the PLR pathway.

# Retinal, optic disc and optic nerve lesions

Unilateral lesions will usually result in impaired vision in the affected eye and loss of the direct and consensual PLR on stimulating the affected eye. Both the direct and consensual PLR should still be present on stimulating the normal eye. Bilateral lesions will usually result in impaired vision, mydriasis and loss of the PLR (both the direct and consensual reflexes) in both eyes.

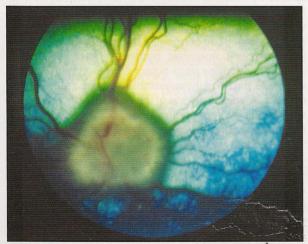
Sudden acquired retinal degeneration: SARD is characterized by an acute loss of vision (although in some cases this may develop over a few days), and occurs occasionally in dogs in the UK (Mattson et al., 1992). Affected dogs are typically adult (middle-aged), can be of pedigree or mixed breed descent, and present bilaterally blind with dilated unresponsive pupils. In the acute stages no abnormalities are evident on ophthalmoscopic examination, but over time (weeks later) a bilaterally symmetrical retinal degeneration becomes evident, with hyper-reflectivity of the tapetal fundus and attenuation of retinal blood vessels. An electroretinogram is required to demonstrate photoreceptor death in the acute stage in order to distinguish SARD from other lesions responsible for acute-onset blindness (Miller et al., 1998). There is no treatment for SARD; although the blindness is permanent, no further clinical signs develop.

Optic disc hypoplasia: Optic disc hypoplasia may be unilateral or bilateral; it occurs sporadically in many dog breeds and has been suggested to be inherited in the Miniature Poodle (Kern and Riis, 1981). Depending on the severity, optic disc hypoplasia may result in decreased to absent vision with decreased PLR proportional to the degree of optic disc hypoplasia. In unilateral cases the owner may not notice the problem. Extreme cases present bilaterally blind with bilaterally dilated and unresponsive pupils from the time that the puppies first open their eyes. On ophthalmoscopic evaluation, affected optic discs appear small and grey in colour (Peterson-Jones, 1995). There is no treatment, but in those cases with a possible hereditary cause preventive measures should be taken against breeding.

Optic disc atrophy: Damage to the retinal ganglion cells or proximal axonal processes may occur due to a variety of causes, including generalized retinal degeneration, glaucoma, trauma and inflammatory lesions. The consequence of this is axonal loss or the development of Wallerian-like degeneration of axons, with loss of the surrounding myelin sheath. The amount of axonal loss determines the degree of optic disc atro-

phy, which appears grey and shrunken-looking on ophthalmoscopic examination. This process is gradual and not immediately apparent at the time of insult.

Papilloedema: Papilloedema is defined as oedema of the optic disc and usually results from raised intracranial pressure (due to cerebral tumours and inflammation) but may occur secondary to optic nerve tumours and inflammation and potentially in conditions causing widespread myelin oedema (seen in certain metabolic and toxic disorders, such as hexachlorophene poisoning). Papilloedema is evident as an irregular and swollen optic disc margin (Figure 9.13), frequently with evidence of retinal congestion and haemorrhage (Palmer et al., 1974). Papilloedema needs to be differentiated from hypermyelination of the optic disc (pseudopapilloedema) where myelination extends beyond the periphery of the optic disc as a normal feature, giving the disc margin an irregular and fluffy appearance. Hypermyelination is more evident in certain large breed dogs, including Boxers, German Shepherd Dogs and Golden Retrievers. The presence of papilloedema (although it is inconsistently present), with evidence of central nervous system (CNS) signs, is a reliable indicator of raised intracranial pressure and suggestive of an increased risk of brain herniation (Saper and Yossleson, 1975). Historically it has been reported that papilloedema spares vision and that this can be used to distinguish it from optic neuritis; however, in the majority of cases in clinical practice, any forebrain or optic nerve lesion severe enough to cause papilloedema will usually interrupt the visual pathways resulting in concurrent visual deficits.



9.13 Papilloedema, with evidence of an irregular and swollen optic disc margin, in a Boxer with a large forebrain tumour. The identification of papilloedema should alert the clinician to the probability of raised intracranial pressure. © Jacques Penderis.

Optic neuritis: Optic neuritis or papillitis is defined as inflammation of the optic nerve and is characterized by visual loss in the presence of optic disc changes similar in appearance to papilloedema and, as such, can be difficult to distinguish from papilloedema on ophthalmoscopic examination (Fischer and Jones, 1972). Typically the optic disc appears swollen, with

frequent haemorrhages. Potential causes (Neaderland, 1989) include granulomatous meningoencephalitis (GME), canine distemper, cryptococcosis (Jergens *et al.*, 1986; Malik *et al.*, 1992) and histoplasmosis (Percy, 1981), though often no underlying cause is identified and the disorder is presumed to be immune-mediated. Many cases will respond to immunosuppressive treatment with steroids; however, relapses are likely and the prognosis for recovery of vision remains guarded (Peterson-Jones, 1995).

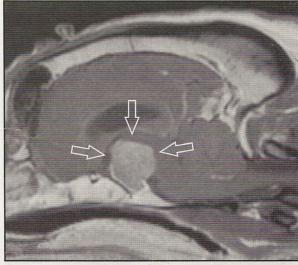
### Miscellaneous causes:

- Neoplasia (primary optic nerve neoplasia versus secondary compressive orbital neoplasms) may interrupt optic nerve function
- Trauma may cause optic nerve compression, traction or haemorrhage
- Retinal degeneration (also known as progressive retinal atrophy) and retinal dysplasia are hereditary in many different breeds of dog and can result from taurine deficiency in cats. The reader is referred to standard ophthalmology textbooks for full details of retinal disease.

## Optic chiasm lesions

Lesions affecting the optic chiasm will usually result in decreased to absent vision and mydriasis with loss of both the direct and consensual PLR in both eyes.

Neoplasia and other space-occupying lesions: Space-occupying masses (see Chapter 8) may occasionally occur at the level of the optic chiasm and, despite the slow development of the underlying disease process, some animals may present with an acute onset of visual deficits (Davidson et al., 1991). Lymphoma is a common cause in cats but consideration should be given to other tumours in dogs and cats, in particular pituitary macroadenomas (Figure 9.14), meningiomas and tumours of the nasal cavity



9.14 MR image appearance of a contrast-enhancing mass (arrows) at the level of the optic chiasm in a dog. The appearance and clinical findings were consistent with a pituitary macroadenoma. © Jacques Penderis.

extending into the region of the optic chiasm. An unusual brain tumour called a suprasellar germ cell tumour has been reported in young adult dogs, in particular Dobermann Pinschers (Valentine *et al.*, 1988) This tumour expands in the region of the pituitary fossa and can become extremely large, causing compression of the optic chiasm and the adjacent cavernous sinus and associated cranial nerves (see Cavernous sinus syndrome, below).

# Miscellaneous causes:

- Vascular lesions, including haemorrhage and vascular malformations
- Inflammatory lesions, e.g. fungal granuloma (see Chapter 10).

## **Optic tract lesions**

Optic tract lesions usually cause visual deficits in the lateral visual field of the contralateral eye and the medial visual field of the ipsilateral eye. The PLR is intact in both eyes but the degree of pupillary constriction may be slightly reduced in the contralateral eye (most evident on the swinging flashlight test).

**Space-occupying masses:** As for other CNS structures, the optic tracts are vulnerable to disruption or compression by mass lesions, including tumours and haemorrhage.

Inflammatory lesions: The most common causes of CNS inflammation affecting the visual tracts in dogs include GME and infectious agents including Toxoplasma and Neospora, canine distemper virus, tickborne agents and Cryptococcus (Chapter 10). In cats, feline infectious peritonitis (FIP) is a significant cause, but consideration should be given to feline leukaemia virus (FeLV), feline immunodeficiency virus (FIV), toxoplasmosis, cryptococcosis and immune-mediated encephalitis.

## Decreased vision with intact PLRs

Lesions affecting the central projections of the visual pathway (from the lateral geniculate nucleus to the visual cortex) will result in visual deficits but do not affect the PLR. The PLR requires fewer intact axons than conscious perception of vision and therefore the situation may occasionally arise that in partial lesions of the proximal visual pathways there is loss of vision but sparing of the PLR, creating the illusion of a more central lesion.

Unilateral lesions affecting the central projections of the visual pathways usually demonstrate a diminished to absent lateral visual field in the contralateral eye and (less obviously) a diminished to absent medial visual field in the ipsilateral eye. Other clinical signs of forebrain disease, including decreased consciousness, seizures, circling, conscious proprioceptive deficits and hemi-neglect/hemi-inattention syndrome (Figure 9.15) would usually be expected in forebrain lesions severe enough to cause visual deficits (see Chapters 2 and 8).



9.15 In cases with severe forebrain disease the visual loss from one visual field may be associated with hemi-neglect/hemi-inattention syndrome contralateral to the lesion, demonstrated here by this dog being unable to perceive the left side of the food bowl and consequently only eating from the right side of the bowl. © Jacques Penderis.

## Degenerative diseases

Central visual disturbances may also be a feature of some degenerative disorders, particularly the lysosomal storage diseases (reported in gangliosidoses and sphingomyelinosis). For further details on these disorders, see Chapters 8 and 12 and Appendix 1.

#### Anomalous diseases

Hydrocephalus: Congenital hydrocephalus, characterized by massive dilation of the ventricular system of the brain and in particular the lateral ventricles, is usually characterized by a dome-shaped forehead (see Chapter 8). In congenital hydrocephalus, and to a lesser extent acquired hydrocephalus, the optic radiations (as they pass adjacent to the lateral ventricles) are particularly vulnerable to injury, and visual deficits are therefore one of the potential clinical signs. Congenital hydrocephalus is further characterized by the presence of bilateral ventrolateral strabismus – the 'setting sun sign' – as discussed under disorders of eyeball position and movement.

Lissencephaly: Lissencephaly is a rare developmental disorder, described in the Lhasa Apso dog, where there is congenital absence of cerebrocortical convolutions. Neurological abnormalities become apparent within the first year of life and include seizures, behavioural abnormalities and visual disturbances (Greene et al., 1976). Treatment is limited to management of seizures, and the prognosis is grave in this progressive disorder.

#### Metabolic diseases

Diffuse encephalopathies, most commonly secondary to metabolic disorders or hypoxic episodes, may present with visual deficits (see Chapter 8). Any animal with a metabolic encephalopathy severe enough to cause visual deficits will usually demonstrate marked CNS depression. Potential metabolic encephalopathies that should be considered include: hepatic encephalopathy,

hypoglycaemia, renal-associated encephalopathy, profound electrolyte derangements, endocrine-associated encephalopathies (hypothyroidism), profound acid—base disturbances and mitochondrial encephalopathies.

Global cerebral ischaemia may occur as a consequence of anaesthetic accidents or following prolonged seizures. Post-ictal depression (functional forebrain suppression following seizure activity) may also present as central blindness. All these diseases are discussed in Chapter 8.

## Neoplastic diseases

Space-occupying lesions within the cerebral hemispheres are primarily tumours. The most common primary brain tumours include meningiomas (particularly in cats) and gliomas, but ependymomas, choroid plexus papillomas and metastatic tumours should also be considered (see Chapter 8 for details of diagnosis and treatment of brain tumours).

## Inflammatory diseases

Immune-mediated (in dogs, particularly GME) and infectious causes (including viral, bacterial, protozoal, rickettsial and fungal agents) of encephalitis should be considered (see Chapter 10 for details of diagnosis and treatment of encephalitis).

#### Traumatic diseases

The forebrain is vulnerable to trauma, though it is relatively well protected (more so in dogs) by the skull and overlying masticatory muscles. Blindness, as one of the potential clinical signs of forebrain trauma, may be evident immediately following the injury or the onset may be delayed in the event of secondary processes, including CNS infection or abscessation.

# Toxic diseases

Toxins are rare causes of cortical blindness, but in the presence of other suggestive clinical signs, particularly gastrointestinal disturbances, lead poisoning should be considered (Zook *et al.*, 1969).

#### Vascular diseases

Although an uncommon cause of blindness, vascular lesions (haemorrhagic or ischaemic in nature) may occur secondary to underlying diseases, including bleeding disorders (Figure 9.16) and trauma (see Chapter 8).



This dog 9.16 presented with an acute onset of blindness and loss of the pupillary light reflex, suggestive of a retinal, optic nerve, optic chiasm or bilateral optic tract lesion. Evidence of scleral haemorrhagesindicated the possibility of an underlying bleeding disorder, and bilateral optic tract haemorrhages were later confirmed as the cause of the blindness. © Jacques Penderis.

# Disorders of pupil size and function

Pupil abnormalities, usually evident as alterations in pupil size, in the absence of visual loss may affect one or both pupils (Figure 9.17). Anisocoria results when only one pupil is affected. In this instance, evaluation of the PLRs is necessary in order to determine which pupil is abnormal. Before any neuro-ophthalmology assessment is performed it is essential first to ascertain whether the pupil abnormalities could be explained by non-neurological abnormalities of the iris (including iris atrophy, iris hypoplasia, uveitis and trauma) or globe (including lens luxation and glaucoma). Painful conditions of the cornea and conjunctiva may also cause miosis. Brief oscillations of pupillary size, referred to as hippus, may occur as a normal feature in response to light exposure. Very exaggerated hippus may be an indication of CNS disease, particularly if it occurs in conjunction with other neuro-ophthalmological abnormalities.

Condition	Miosis or mydriasis	Always bilateral?
Topical pharmacological agents	Either	No
Resting anisocoria	Either	No
Horner's syndrome	Miosis	No
Static anisocoria (spastic pupil)	Miosis	No
Organophosphate toxicity	Miosis	Yes
Hemidilated pupil (D-shaped pupil)	Mydriasis	No
Cavernous sinus syndrome	Usually mydriasis (or mid-range non-responsive)	No
Pupillotonia	Usually mydriasis	No
Cerebellar disease	Mydriasis	No
Raised intracranial pressure progressing to herniation	Initial miosis, later mydriasis (see Chapters 8 and 19)	Initially may be unilateral, but usually bilateral
Dysautonomia	Mydriasis	Yes
Thiamine deficiency	Mydriasis	Yes

9.17 Causes of alterations in pupil size and function that are not usually associated with loss of vision (with the exception of raised intracranial pressure).

## Pharmacological miosis and mydriasis

Pharmacological agents, accidentally or intentionally administered, may profoundly affect pupillary function. This includes pupillary dilation following administration of mydriatic (e.g. atropine) and cycloplegic (e.g. tropicamide) drugs and pupillary constriction following administration of miotic drugs (e.g. pilocarpine). Systemically administered anaesthetic agents may also have a profound effect on pupillary size, such as the miosis evident following systemic administration of some opioid agents in dogs (Stephan *et al.*, 2003).

# Resting anisocoria (idiopathic anisocoria)

Subtle resting anisocoria is a common observation, particularly in cats, and is of no clinical significance. The anisocoria is similar to physiological anisocoria seen in up to 20% of the human population (Lepore, 2002) and is thought to be the consequence of an imbalance in basal sympathetic and parasympathetic tone between the two eyes.

#### Horner's syndrome

Lesions affecting the sympathetic supply to the head will result in Horner's syndrome (Figure 9.18) and loss of cutaneous vascular tone on the affected side with peripheral vasodilation. The loss of cutaneous vascular tone in dogs and cats is evident as increased cutaneous temperature (the pinna on the affected side being warmer than the unaffected side), hyperaemia and anhydrosis (decreased sweating on the affected side of the head). The effects of loss of cutaneous vascular tone on the eye include mild congestion of the scleral blood vessels and decrease in intraocular pressure. Horner's syndrome describes the specific ophthalmic changes associated with loss of sympathetic innervation; these include:

- Miosis (constriction of the affected pupil): avulsion of the brachial plexus nerve roots will usually cause only a partial Horner's syndrome, often with miosis as the only feature. This is usually because only the T1 nerve root of the T1-T3 sympathetic outflow is affected by brachial plexus avulsions. Partial Horner's syndrome (with miosis as the only feature) may also occur in dogs with acute and severe lateralized cervical spinal cord disease but the expectation would still be for the majority of cases to have a complete Horner's syndrome (Griffiths, 1970)
- Enophthalmos: loss of sympathetic innervation leads to loss of orbital smooth muscle tone and sinking of the globe into the orbit
- Protrusion of the third eyelid (nictitating membrane): while in the dog this occurs passively secondary to enophthalmos, in the cat



9.18 Left Horner's syndrome demonstrating miosis, ptosis and protrusion of the third eyelid. Enophthalmos is the fourth feature associated with Horner's syndrome but cannot be appreciated on this image. © Jacques Penderis.

- the protrusion is due to a combination of enophthalmos and loss of third eyelid retraction
- Ptosis (drooping) of the upper eyelid and decreased tone of the lower eyelid: this occurs as a result of loss of smooth muscle tone affecting the Müller's muscle.

Horner's syndrome is usually classified according to the level of the lesion along the sympathetic pathway (see Figure 9.11) as first order, second order (preganglionic) or third order (post-ganglionic). Pharmacological testing or evidence of other neurological abnormalities can be used to localize the site of the lesion but the times to a response should only be treated as a guide to the site of the lesion and other neurological signs should be taken into consideration. In the majority of cases with apparent third order Horner's syndrome (based on pharmacological testing) no underlying cause can be identified and these cases have historically been termed idiopathic Horner's syndrome (Kern et al., 1989; Morgan and Zanotti, 1989). The prognosis depends to a large degree on the underlying neurological disease but is excellent in idiopathic Horner's syndrome. The disorder in idiopathic Horner's syndrome is largely cosmetic and in many cases may resolve spontaneously. Treatment is rarely required but in cases with bilateral Horner's syndrome (Figure 9.19) and where vision is obscured by the third eyelid protrusion, topical 10% phenylephrine can be used to provide occasional, short-term alleviation of the symptoms. Maximal effect occurs for up to 2 hours and in some cases the effect may be maintained for up to 18 hours.



Bilateral Horner's syndrome in a Golden Retriever. The third eyelid protrusion may interfere with vision in bilateral Horner's syndrome; in unilateral Horner's syndrome it can be considered mainly cosmetic.

© Jacques Penderis.

Pharmacological testing of Horner's syndrome: In cases where Horner's syndrome has been present for some time (usually at least 2 weeks), denervation hypersensitivity resulting from the sympathetic denervation allows prediction of the site of the lesion based on increased sensitivity to topical phenylephrine. The time to pupillary dilation, following administration of 1% phenylephrine topically in both eyes, is determined. Essentially, the shorter the time to pupillary dilation, the closer is the lesion to the iris.

- Less than 20 minutes suggests third order Horner's syndrome.
- 20 to 45 minutes suggests second order Horner's syndrome.
- 60 to 90 minutes suggests first order Horner's syndrome or no sympathetic denervation of the eye.
- If 10% phenylephrine is used, mydriasis occurs in 5–8 minutes in post-ganglionic (third order neuron) lesions (Figure 9.20).



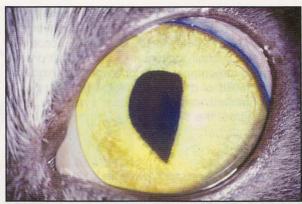
9.20 Following topical administration of 10% phenylephrine into the right eye of the bilateral Horner's syndrome case from Figure 9.19, the miosis resolved rapidly (in less than 8 minutes), indicating a third order neuron lesion in the right eye. © Jacques Penderis.

# Static anisocoria (spastic pupil syndrome)

Static anisocoria occurs in cats and is associated with FeLV infection, though it has been suggested to occur in association with other viruses, including FIV. However, few documented cases of static anisocoria or hemidilated pupils are recorded in the literature (Brightman et al., 1977, 1991) and the majority of textbooks referring to the disorder provide largely anecdotal evidence. Cats with static anisocoria demonstrate moderate miosis (occasionally cats may demonstrate mydriasis) and anisocoria. The miosis typically only changes minimally, if at all, during dark adaptation. The clinical signs may be intermittent or change during the course of the disease and are thought to be the result of either viral infection or lymphosarcoma infiltration of the short ciliary nerves or ciliary ganglion. See also Hemidilated pupil (D-shaped pupil) below.

# Hemidilated pupil (D-shaped pupil)

Hemidilated pupil is the consequence of vulnerability to paralysis of the ciliary nerves supplying the iris constrictor muscles in cats, in particular to FeLV-associated lymphosarcoma infiltration. Either of the two ciliary nerves, the lateral (malar) ciliary nerve or medial (nasal) short ciliary nerve, may be affected and, depending on which one is affected, this results in either a D-shaped or a reverse D-shaped pupil (Figure 9.21).



9.21 Reverse D-shaped pupil in a cat, indicating damage to the nasal ciliary nerve of the left eye. Cats presenting with ciliary nerve damage should be investigated for FeLV, as well as other viral agents and lymphoma. (© Comparative Ophthalmology Unit, Animal Health Trust.)

# Organophosphate and carbamate toxicity

Alterations in pupil size are a feature of a variety of toxins, with the most common being the marked miosis associated with organophosphate and carbamate toxicity. Both drugs inhibit cholinesterase and induce a variety of clinical signs, including salivation, gastro-intestinal disturbances, muscle twitching, weakness and possibly seizures (see Chapters 8 and 12).

### Cavernous sinus syndrome

The paired cavernous sinuses are situated on the floor of the calvarium and adjacent to the pituitary gland. This area offers a convenient site for expansion of mass lesions (particularly tumours but also inflammatory lesions and vascular malformations) and, as it is the venous drainage from the frontal sinus and nose, there may be an increased likelihood of infectious and neoplastic diseases of these structures spreading to the cavernous sinus area. Neurological deficits develop when these lesions expand to incorporate the adjacent cranial nerves III, IV and VI (innervating the extraocular muscles, iris and ciliary muscle), the first two branches of the trigeminal nerve and the postganglionic (third order) sympathetic supply to the eye. It is reported that cavernous sinus syndrome affects the ophthalmic and maxillary branches of the trigeminal nerve (Theisen et al., 1996) but in practice lesions may expand and involve the mandibular branch of the trigeminal nerve as well.

Mass lesions in this area may therefore result in paralysis of the extraocular muscles (external ophthalmoplegia), loss of iris and ciliary muscle function (internal ophthalmoplegia), ipsilateral sensory deficits in the ophthalmic and maxillary branches of the trigeminal nerve and, with particularly large lesions, atrophy of the ipsilateral masticatory muscles (innervated by the mandibular branch of the trigeminal nerve) with associated sensory deficits. The potential for involvement of both the parasympathetic (CN III) and sympathetic innervation of the pupil can produce either a fixed mydriatic or a mid-range pupil. Paralysis of the extraocular muscles, the ciliary muscle and the parasympathetic and sympathetic supply to the iris is

termed total ophthalmoplegia or panophthalmoplegia. Because the optic nerve is distant from the cavernous sinus, vision is not lost, but the loss of lens accommodation and eyeball movement would impair vision. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain should be performed in any animal with cavernous sinus syndrome, after retropulsion of the eyeball to ensure that the lesion is not retrobulbar.

## **Pupillotonia**

Pupillotonia (defined as a pupil that is slow to react to light on both direct and consensual stimulation) has been reported in the dog due to a suspected immune-mediated cause (Gerding *et al.*, 1986). This condition has not been reported since and may simply have represented a poor light source, fear or iris atrophy.

# Cerebellar disease

Mydriasis of the contralateral pupil is an uncommon feature of the syndrome of clinical signs associated with asymmetrical cerebellar disease (DeLahunta, 1983) (see Chapter 12). This may also serve to explain the intermittent mydriasis seen in cats with feline spongiform encephalopathy in addition to the diffuse cerebellar signs and altered behaviour.

## Raised intracranial pressure

The oculomotor nerve, as it passes ventral to the brain and over the petroclinoid ligament, is vulnerable to compression as a result of dramatic increases in intracranial pressure (ICP) due to neoplastic, traumatic and inflammatory CNS lesions. Initial irritation of the oculomotor nerve as a result of raised intracranial pressure is evident as a miotic pupil, but this rapidly progresses to complete paralysis with a fixed dilated pupil with continuing elevation of intracranial pressure and herniation of the cortex under the tentorium. Such animals are usually comatose. Extensive lesions that affect the sympathetic innervation as well as the oculomotor nerve result in mid-position fixed pupils. See Chapters 8 and 19 for further information on the pathophysiology, assessment and treatment of raised ICP.

## Dysautonomia

Bilateral pupillary dilation that is not responsive to light, protrusion of the third eyelids and decreased tear production, in the presence of normal vision, are features of canine and feline dysautonomia (also called Key-Gaskell syndrome in cats) (Figure 9.22) (Wise and Lappin, 1990). The ocular changes are also associated with profound systemic signs of autonomic dysfunction (and, in particular, depression, anorexia, decreased saliva production, megaoesophagus, bradycardia and occasionally faecal and urinary incontinence). The canine and feline syndromes are both rare and occur sporadically. The treatment is purely supportive and the prognosis is guarded (for a more indepth discussion see Chapter 18). Pharmacological testing may be useful to confirm sympathetic and parasympathetic dysfunction.



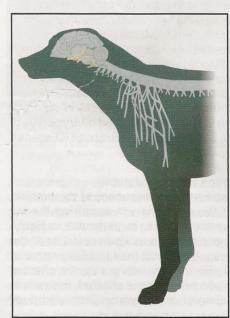
9.22 Feline dysautonomia with protrusion of the third eyelids, pupillary dilation and drying of the nose. (Courtesy of the Royal (Dick) Veterinary School.)

# Thiamine (vitamin B<sub>1</sub>) deficiency

Bilateral pupillary dilation with the occasional presence of non-specific fundus changes, including peripapillary oedema and papillary neovascularization, are evident in thiamine (vitamin  $B_1$ ) deficiency in cats. The ocular changes occur in conjunction with systemic changes of anorexia, ataxia and cervical ventroflexion. The prognosis is good with thiamine supplementation (see Chapter 10).

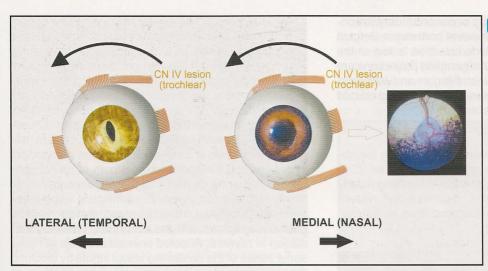
# Disorders of eyeball position and movement

As discussed previously, there is an intimate functional association between the innervation to the extraocular muscles and the vestibular system. The extraocular muscles are innervated by CN III (oculomotor), CN IV (trochlear) and CN VI (abducent) (Figure 9.23). Any strabismus due to a lesion in one or more of these cranial nerves must be differentiated from lesions affecting the extraocular muscles (including traumatic rupture and extraocular myositis).



#### 9.23

Lesion localization for ocular abnormalities; cranial nerves II, III, IV and VI are highlighted. The sympathetic supply to the eyes is not shown.



Trochlear nerve 9.24 lesions in isolation are extremely rare (they usually occur in conjunction with CN III and VI lesions) but would manifest as rotation of the eveball, with the dorsal portion (12 o'clock position) of the eyeball deviated temporally (laterally). This is apparent in cats as rotation of the vertical pupil, but in dogs with round pupils the rotation is apparent only on fundic evaluation of the dorsal retinal arteriole and vein. (Reproduced from In Practice; © Jacques Penderis)

- Lesions simultaneously affecting CNs III, IV and VI result in external ophthalmoplegia, and internal ophthalmoplegia if the pupillary constrictor (CN III) is affected.
- Lesions with only CN III involvement may present with a ventrolateral strabismus; more rarely lesions may only affect single muscle groups, resulting in a strabismus opposite to the normal function of the denervated muscle.
- Lesions affecting the trochlear nerve in isolation are extremely rare but, where they do occur, will result in loss of function of the ipsilateral dorsal oblique muscle (brainstem lesions may result in loss of function, ipsilateral or contralateral). The dorsal oblique muscle functions to rotate the dorsal portion of the globe nasally (intortion); lesions of the dorsal oblique muscle are therefore evidenced by rotation of the eyeball, with the dorsal portion of the eyeball deviated temporally (laterally). In cats this is evident as rotation of the normally vertical pupils, but in dogs, with a round pupil, this is only apparent on demonstrating lateral deviation of the dorsal retinal arteriole and vein on ophthalmoscopic examination (Figure 9.24).
- Abducent lesions are extremely rare in isolation but, where they do occur, will result in medial strabismus of the affected eye (the abducent nerve innervates the lateral rectus and retractor bulbi muscles of the eyeball). Lesions of the abducent nerve can be distinguished from congenital medial strabismus by the absence of eyeball retraction in the affected eye on performing the corneal reflex (Figure 9.25).

Eyeball movement is further controlled by the vestibular and saccadic systems. The function of the vestibular system with regard to vision is to maintain the visual image in a steady position on the retina in response to movements of the head. This is achieved by inducing eye movements, via the vestibulo-ocular reflex, that are equal to but in the opposite direction to the head movements. In contrast to the vestibular system, the saccadic system functions to change the



9.25 Lesions of the abducent nerve will cause medial strabismus but can easily be differentiated from the congenital medial strabismus in this crossbred dog by the absence of eyeball retraction on performing the corneal reflex in abducent nerve lesions. © Jacques Penderis.

line of sight to focus a new visual stimulus on the retinal region with the highest visual acuity (usually the area centralis). Saccadic eye movements occur in response to startle reflexes (sudden visual and auditory stimuli) and during the fast-phase eye movements of the vestibulo-ocular reflex.

#### Congenital nystagmus

Congenital nystagmus may be recognized in association with ocular abnormalities and congenital visual deficits but occasionally nystagmus may be present in the absence of other ocular abnormalities (Peterson-Jones, 1995). The nystagmus associated with congenital visual deficits is characterized as a continuous fine oscillation of both globes, often rotatory, or may be characterized as random eye movements (amaurotic nystagmus or 'searching nystagmus'). Rotary nystagmus has been described in association with microphthalmos and congenital cataracts in puppies, even though vision is not totally lost. Animals that lose their vision at a young age may develop nystagmus (Ferreira and Peterson-Jones, 2002).

Pendular nystagmus may occur secondary to congenital abnormalities of the visual pathway in Belgian Sheepdogs. In these dogs decussation is lost at the optic chiasm and all the retinal ganglion projections are into the ipsilateral optic tract (Hogan and Williams, 1995). Congenital nystagmus in Siamese and related cat breeds is discussed below.

## Congenital strabismus

Congenital strabismus is seen occasionally in the absence of identifiable underlying causes (Figure 9.26) or may be associated with albinism (see Congenitally abnormal visual pathways in Siamese and related breeds), congenital vestibular syndrome or brachycephalic breeds.



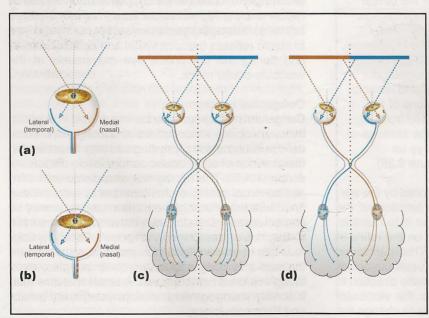
9.26 Congenital divergent strabismus (exotropia) in a Golden Retriever puppy. © Jacques Penderis.

# Congenitally abnormal visual pathways in Siamese, Birman and Himalayan cats

Albino and imperfect albino animals (including Siamese, Birman and Himalayan coat cats) demonstrate congenital abnormalities of the visual pathways (Cucchiaro,

1985; Bacon et al., 1999) (Figure 9.27). The consequent clinical anomalies demonstrated in the Siamese and related breeds include convergent strabismus (esotropia) (Figure 9.28) and occasionally spontaneous pendular nystagmus. The majority of the axonal projections from the temporal retina usually do not cross at the level of the optic chiasm, but in melanindeficient animals there is increased cross-over of these normally uncrossed pathways at the optic chiasm. It is likely that melanin or a closely linked gene is important in determining the correct axonal path of retinal ganalion cells during development. The consequence of this abnormal cross-over is that conflicting visual information from both visual fields is mapped at each lateral geniculate nucleus, with the abnormally crossed information in reverse. Affected animals are able to make some sense of the conflicting visual inputs by blocking the projections of the inappropriately crossed afferents into the visual cortex and thus restore some vision. The consequence, however, is that the consciously perceived visual field and binocularity is reduced (see Figure 9.27).

Although the visual cortex projections of the misrouted visual afferents are blocked, this information is still available for the reflex control of eyeball position and this may explain both the convergent strabismus and occasional spontaneous nystagmus present in these cases. An alternative explanation for the convergent strabismus may be the result of a compensatory attempt to obtain increased overlap of the left and right visual fields. The spontaneous nystagmus is the consequence of the misrouted information being mapped in reverse at the level of the lateral geniculate nucleus. If an animal uses this misrouted and reversed information during attempts to fix the gaze on a visual target, the consequent eyeball pursuit movements are inverted and the eye moves in the opposite direction to the target movement. Repeated eyeball pursuit movements in the wrong direction are then made, resulting in nystagmus.



Simplified representation of 9.27 the visual pathway abnormalities in the Siamese and related cat breeds. (a) In normal animals the temporal retinal afferents (blue) do not cross at the optic chiasm. (b) In Siamese and related cat breeds information from the temporal retina is abnormally crossed at the optic chiasm. (c) This misrouted information is then mapped to the wrong lateral geniculate nucleus and visual cortex. (d) Affected cats compensate by blocking the cortical projections of the incorrect afferent at the level of the lateral geniculate nucleus but their perceived visual field and consequently binocularity are dramatically reduced. This inappropriately crossed visual information is still used for eyeball position and visual tracking, which may explain the medial strabismus and abnormal nystagmus. (Reproduced from In Practice; O Jacques Penderis)



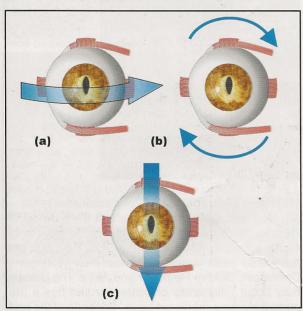
9.28 Convergent strabismus (esotropia) in a Siamese cat with congenital abnormalities of the visual pathways. (Reproduced with permission from Penderis, 2003)

# Divergent strabismus (exotropia) in brachycephalic breeds

Congenital divergent strabismus (exotropia), which may be unilateral or bilateral, occurs in brachycephalic breeds, including the Boston Terrier, English Bulldog and Pekingese. Vision and eye movements are normal and the condition appears non-progressive. Although no cause has been identified, paresis or abnormal caudal insertion of the medial rectus muscle have been suggested as possible explanations.

#### Vestibular disease

Disorders affecting the vestibular system (discussed in more detail in Chapter 10) may result in alterations in eyeball position and movement, typically the presence of nystagmus and/or strabismus. Nystagmus is categorized as vertical, horizontal or rotatory (Figure 9.29).



9.29 Spontaneous nystagmus associated with vestibular disease may indicate the site of the lesion. Horizontal (a) and rotatory (b) nystagmus is seen in both peripheral and central vestibular disease but vertical (c) nystagmus is only associated with central vestibular disease. (Modified from Penderis, 2003c.)

In vestibular disease the strabismus is characteristically ventrolateral in direction and can be induced or exacerbated by holding the animal's head with the nose elevated (Figure 9.30). Bilateral vestibular disease may cause bilateral ventrolateral strabismus on elevating the head (Figure 9.31).



9.30 Ipsilateral ventrolateral strabismus induced by raising the head, seen in the right eye of this Shih Tzu, is a frequent feature of vestibular disease.

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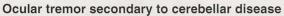
9.31 Bilateral vestibular disease may demonstrate bilateral ventrolateral strabismus on raising the head, seen in this Boxer. © Jacques Penderis.

# Congenital hydrocephalus

In addition to the visual deficits associated with hydrocephalus under decreased vision with intact PLRs, congenital hydrocephalus is further characterized by the presence of bilateral ventrolateral strabismus – the 'setting sun sign' (Figure 9.32) (Harrington *et al.*, 1996). This ventrolateral strabismus may be the result of conformation changes of the skull and orbit secondary to the hydrocephalus, with affected puppies usually developing a domed skull with open calvarial sutures, but is more likely to be secondary to compression of CN III, as the strabismus frequently resolves some time following the placement of a corrective ventricular shunt (see Chapter 8).



9.32 Congenital hydrocephalus is associated with a bilateral ventrolateral strabismus, the so-called 'setting-sun sign', as seen in this 3-month-old Pug puppy with blindness and depression. © Jacques Penderis.



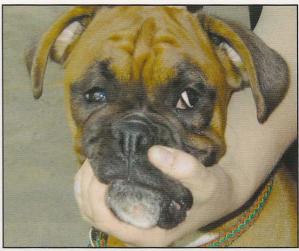
A fine ocular tremor, usually only evident on ophthalmoscopic assessment, may be a feature of diffuse cerebellar disease. This is thought to be a form of cerebellar intention tremor affecting the extraocular muscles.

#### Cavernous sinus syndrome

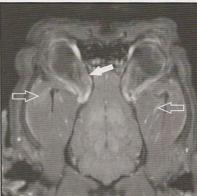
Cavernous sinus syndrome is the most common cause of either external ophthalmoplegia (paralysis of the extraocular muscles) or total ophthalmoplegia (paralysis of the extraocular muscles, iris and ciliary muscles). Cavernous sinus syndrome is discussed under Disorders of pupil size and function, above.

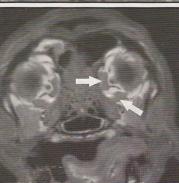
## Extraocular myositis

Inflammation of the extraocular muscles, with a presumed underlying immune-mediated aetiology similar to that of masticatory myositis, occurs occasionally in dogs (see Chapter 11). During the acute inflammatory phase, affected dogs present with exophthalmos, strabismus and decreased range of eyeball movement due to the swelling of the extraocular muscles (Figure 9.33). During the chronic stage of the inflammatory disease, muscle tissue is largely replaced by fibrosis and then (although the exophthalmos resolves) marked strabismus often develops. Diagnosis is by demonstrating enlargement and sometimes oedema of the extraocular muscles on MRI (Figure 9.34) and ultrasound examination, demonstrating elevated muscle enzyme levels and confirming inflammatory changes on muscle biopsy (Ramsey et al., 1995). Although biopsy of the extraocular muscles is difficult, extraocular myositis may occur as part of a wider polymyositis and therefore biopsy of the readily accessible masticatory muscles is useful in some cases. Because of the presumed underlying immune-mediated aetiology, the disorder often responds to corticosteroid therapy (Carpenter et al., 1989). For details of treatment protocols, see Chapter 11 (masticatory myositis) and Chapter 17 (polymyositis).



9.33 Lateral strabismus in a case with acute extraocular myositis. Fibrosis of the extraocular muscles, once the acute inflammation has resolved, may also result in strabismus. © Jacques Penderis.





9.34 image appearance of the acute stage of extraocular myositis, demonstrating enlargement of the extraocular muscles (solid arrows). More widespread inflammation is evident in the masticatory muscles in this case (open arrows), allowing a confirmatory muscle biopsy to be obtained from this more accessible site. © Jacques Penderis.

## Fibrosing esotropia (Shar Pei strabismus)

Myositis and subsequent fibrosis of the extraocular muscles (with the medial rectus muscle most commonly affected) occur in young Shar Pei dogs and have also been described in the Irish Wolfhound, Dalmatian, Golden Retriever and Akita. The disease may occur unilaterally or bilaterally and has a presumed immune-mediated basis. Because of the preferential involvement of the medial rectus muscle, affected dogs present with convergent strabismus (esotropia) and enophthalmos. The esotropia is often so severe that the cornea is obscured by the conjunctiva and vision is consequently impaired (Figure 9.35).



## 9.35

Fibrosing esotropia in a Shar Pei. The severe convergent strabismus (esotropia) means that the pupils are occluded behind the medial canthus. © Jacques Penderis.

Cases may respond to immunosuppressive levels of corticosteroids but surgical resection may be required in the presence of severe fibrosis of the medial rectus muscle (Gelatt, 2000).

# Retrobulbar swelling or trauma

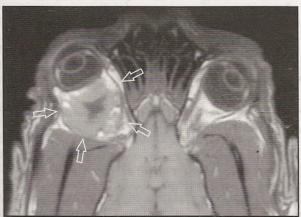
Retrobulbar swelling or mass effect may interfere with normal eyeball movement, with affected cases usually presenting with exophthalmos, protrusion of the third eyelid (Figure 9.36) and occasionally mechanical strabismus (Figure 9.37) (Gilger *et al.*, 1992).



# 9.36

Left retrobulbar mass.
Exophthalmos, protrusion of the third eyelid and mild lateral strabismus were evident in this case.

© Jacques Penderis.



9.37 MR image appearance of a retrobulbar mass (arrows) causing exophthalmos and interfering with normal eyeball movement. © Jacques Penderis.

#### **Tetanus**

Although the clinical signs of tetanus (see Chapter 14) are usually characteristic, strabismus (Figure 9.38) and brief, intermittent protrusion of the third eyelid may occur (Timoney *et al.*, 1988).



9.38 Typical appearance of tetanus with the ears held close together and the forehead wrinkled. Dogs with tetanus may demonstrate lateral strabismus (as in this case), intermittent protrusion of the third eyelids and photophobia. © Jacques Penderis.

## Intracranial lesions causing strabismus

Intracranial lesions may selectively affect the innervation to certain extraocular muscles, resulting in a strabismus. Forebrain lesions causing circling and a head turn may be associated with a lateral strabismus in the direction of the head turn (Figure 9.39). The mechanism for this is uncertain; either it may reflect loss of the innervation to the extraocular musculature (in particular CN III) as a result of raised intracranial pressure, or the neurological deficits responsible for the head turn may in turn induce a lateral strabismus.



9.39 This animal has a right head turn due to a right forebrain lesion, but if the head is held facing forward then a lateral strabismus develops in the direction of the head turn. © Jacques Penderis.

# Disorders of blink

Abnormalities of the blink are usually the result of lesions affecting CN V (trigeminal) or CN VII (facial). The integrity of the blink pathway is evaluated by performing the palpebral reflex (afferent touch sensation via the trigeminal nerve and efferent motor function via the facial nerve) and the menace response (afferent

visual stimulus via the optic nerve and efferent motor function via the facial nerve).

# Abnormalities of blink due to a sensory (CN V or trigeminal nerve) lesion

Lesions of the ophthalmic branch of the trigeminal nerve will result in loss of sensation to the cornea and medial canthus of the eye (as well as the nasal cavity). The consequence of this is loss of the corneal and palpebral reflexes. The menace response should still be intact if vision and the facial nerve are not involved. Exposure keratopathy, with rapid progression from neuroparalytic keratitis to ulcerative keratitis (Figure 9.40), is a frequent complication of ophthalmic branch lesions but is infrequently seen following facial nerve (motor) lesions. Although basal tear secretion should be normal, reflex tear production in response to stimulation of the cornea or nasal mucosa is lost as this is mediated through the ophthalmic branch of the trigeminal nerve. If the mandibular branch of the trigeminal nerve is affected, pronounced enophthalmos may develop as the masticatory muscles atrophy, resulting in an increased retrobulbar space (Figure 9.41).

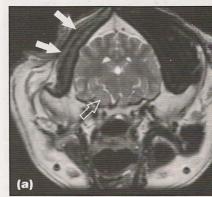


9.40 Neurogenic corneal ulcer (neuroparalytic keratitis) secondary to loss of corneal sensation due to a lesion affecting the ophthalmic branch of the trigeminal nerve. (Reproduced from Penderis (2002) with the permission of Elsevier; original image courtesy of Comparative Ophthalmology Unit, Animal Health Trust)



9.41 Enophthalmos with protrusion of the third eyelid secondary to masticatory muscle atrophy as a result of a lesion affecting the mandibular branch of the trigeminal nerve. © Jacques Penderis.

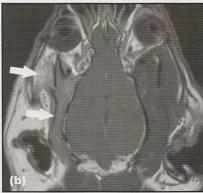
Neoplasia (in particular of the trigeminal nerve roots) is the most common cause of trigeminal nerve lesions (Figure 9.42) but other possibilities should be considered, including trauma, fractures of the petrous temporal bone, inflammatory lesions and cranial polyneuropathies.



# **9.42** MR imag

MR images demonstrating a tumour (a) of the trigeminal nerve root (open arrow) and consequent atrophy of the masticatory muscles (a,b) on the affected side (closed arrows).

© Jacques Penderis.



# Abnormalities of blink due to a motor (CN VII or facial nerve) lesion

One of the functions of the facial nerve is innervation of the orbicularis oculi muscle, which is responsible for closing the eyelids. Decreased to absent function of the orbicularis oculi muscle results in decrease to loss of the menace response and palpebral reflex. The normal retraction of the globe during the corneal reflex is maintained if the trigeminal nerve is preserved. The blink is responsible for spreading the tear film over the cornea and loss of the blink may therefore predispose to an exposure keratitis, though this is more common when there is concurrent reduced tear production or trigeminal nerve damage. Facial nerve lesions are discussed in more detail under disorders of the cranial nerves (Chapter 11). Neurogenic keratoconjunctivitis sicca is discussed below, under disorders of lacrimation.

## Hemifacial spasm

Hemifacial spasm, an unusual syndrome in dogs, is characterized by spasm of the muscles innervated by the facial nerve on one side, resulting in blepharospasm, contraction of the upper lip, elevation of the ear and deviation of the nasal philtrum to the affected side (Figure 9.43). The condition is usually intermittent and as such can often be induced by stimulation of the face on the affected side (Roberts and Vainisi, 1967; Parker et al., 1973) (see also Chapter 11).



9.43 Right-sided hemifacial spasm in a Golden Retriever. In contrast to facial nerve paralysis there is increased muscle tone on the affected side of the face, with the lip and ear pulled up in contrast to the normal left side. Although not apparent in this case, hemifacial spasm often causes a narrowed palpebral fissure on the affected side. © Jacques Penderis.

Disorders of eyelid opening

Ptosis may be evident in both lesions of CN III (oculomotor) and of the sympathetic supply (Horner's syndrome). The ptosis seen in CN III (oculomotor) lesions is due to loss of innervation to the levator palpebrae superioris muscle and is easily differentiated from the ptosis seen in Horner's syndrome, primarily through the difference in pupil size (miosis in Horner's syndrome and mydriasis in oculomotor nerve lesions).

# Disorders of the third eyelid

Protrusion of the third eyelid may occur passively following a loss of sympathetic tone to the orbit (Horner's syndrome and systemic illness), in conditions causing enophthalmos and secondary to retrobulbar masses. Intermittent, brief protrusion of the third eyelid may occur in tetanus (Timoney *et al.*, 1988).

# Haw's syndrome in young cats

Haw's syndrome is bilateral protrusion of the third eyelid of unknown cause and occurs in young cats in the absence of other systemic and ophthalmic abnormalities. It has been suggested to occur in dogs and in particular the Golden Retriever (Gelatt, 2000). The condition may develop following a history of diarrhoea and generally persists for some time before gradually resolving. Although treatment is usually not necessary, either topical 1–2% epinephrine or 10% phenylephrine to abolish the third eyelid protrusion (by stimulating smooth muscle contraction), or 1% atropine to dilate the pupil, has been suggested if the third eyelid protrusion is severe enough to cause visual impairment (Gelatt, 2000, 2001).

## Disorders of lacrimation

The normal production of tears can be subdivided into two components: basal tear production (evaluated by a Schirmer II test, where tear production following anaesthesia of the cornea is measured); and induced tear production (evaluated by a Schirmer I test, where the cornea is not anaesthetized and as a consequence the corneal stimulation from placing the test strip in the eye induces reflex tear production). Induced tear production occurs following stimulation of the ophthalmic branch of the trigeminal nerve (which innervates the surface of the cornea and the nasal mucosa) and in response to high light intensities. Loss of induced tear production most commonly occurs due to lesions of the ophthalmic branch of the trigeminal nerve (DeHaas, 1962), but the decreased tear production is less important than the loss of corneal sensation with consequent decreased blink frequency and development of neuroparalytic keratitis.

#### Lesions resulting in decreased tear production

The lacrimal gland is innervated by the parasympathetic portion of the facial nerve, a branch of which also innervates the lateral nasal gland (a serous-secreting gland that functions to keep the nose moist). Lesions affecting the parasympathetic portion of the facial nerve therefore result in neurogenic keratoconjunctivitis sicca (as both basal and reflex tear production are lost) and an ipsilateral xeromycteria (dry nose) (Figure 9.44). The presence of an ipsilateral dry nostril allows differentiation from immune-mediated keratoconjunctivitis sicca, as nasal mucosa hydration is dependent on the function of the lateral nasal gland and not on tear production. The majority of cases resolve spontaneously if the underlying disorder is addressed (most commonly middle-ear lesions), but supportive management with supplementation of eye lubrication is essential. Because there is no underlying immune-mediated process, ciclosporin A is unlikely to have any effect in neurogenic keratoconjunctivitis sicca. The presence of denervation hypersensitivity following parasympathetic denervation of the lacrimal gland allows the opportunity to re-establish lacrimation in cases that do not spontaneously resolve with a direct-acting parasympathomimetic. The drug most commonly used is 1% pilocarpine, given in the food twice daily, but the dose should be carefully titrated to achieve an effect that stimulates tear production but avoids the development of deleterious side effects, such as vomiting and diarrhoea.



9.44 Left facial nerve paralysis with involvement of the parasympathetic innervation to the lacrimal gland and the lateral nasal gland, resulting in neurogenic keratoconjunctivitis sicca and ipsilateral xeromycteria (dry nose). (© Comparative Ophthalmology Unit, Animal Health Trust.)

## Lesions resulting in increased tear production

Paradoxical tearing (gustrolacrimal reflex or 'crocodile tears') describes the syndrome of excessive tear production while eating or during anticipation of a meal. The syndrome has been recognized for a considerable time in humans (Lutman, 1947) and was subsequently described in the cat (Hacker, 1990). The underlying cause in human medicine is thought to be aberrant regeneration of facial nerve fibres following trauma, with fibres that usually innervate the salivary glands being misrouted to the lacrimal gland. The name 'crocodile tears' was derived from the popular myth that crocodiles cry while eating their prey.

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# **Head tilt and nystagmus**

Karen R. Muñana

# Introduction

Head tilt and nystagmus are relatively common presentations in veterinary practice. These signs are typically associated with vestibular disease, although an intermittent head tilt alone may be due to otitis externa or other aural irritation. A thorough neurological evaluation is critical to successful management; by determining the location of the disturbance within the vestibular system, a list of differential diagnoses and a diagnostic plan can be formulated, in conjunction with recommendations on appropriate treatment and an accurate prognosis.

# **Clinical signs**

 Head tilt is described as a rotation of the head about the atlas (C1) vertebra, such that one of the ears is held lower than the other (Figure 10.1). Head tilt is indicative of vestibular disease and is the most consistent sign of a unilateral vestibular deficit.



Left-sided head tilt in a cat.

 Nystagmus is a term used to denote involuntary rhythmic oscillation of the eyeballs.

 Jerk nystagmus, in which the eye movements have a slow phase in one direction and a rapid recovery in the opposite direction, is commonly seen with vestibular disease.

 Pendular nystagmus is characterized by small oscillations of the eyes with no fast or slow component.

Nystagmus that is observed when the head is in a normal static position is called a spontaneous or

resting nystagmus, whilst that elicited by moving the head into an unusual position is termed a positional nystagmus.

Nystagmus seen in vestibular disease can be horizontal, rotary or vertical in character, and is named according to the direction of the rapid recovery or fast phase of movement (see Chapter 9).

The jerk nystagmus characteristic of vestibular disease must be differentiated from the less common pendular nystagmus, which is most often observed as an incidental finding in Siamese, Birman and Himalayan cats. Pendular nystagmus is a manifestation of a congenital abnormality in the visual pathway, in which a larger percentage than normal of optic nerve axons cross in the chiasm. It can occasionally be seen with cerebellar disease and with visual deficits. Additional discussion on nystagmus can be found in Chapter 9.

Other clinical signs of vestibular dysfunction include:

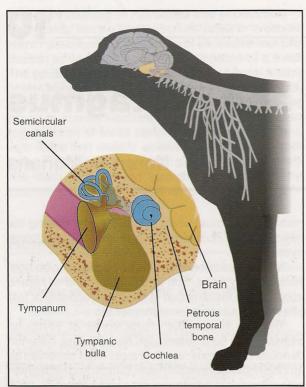
- Ataxia
- Wide-based stance
- Circling, leaning, falling or rolling towards the side of the head tilt
- Positional strabismus, i.e. the eye on the affected side deviates ventrally or ventrolaterally when the head is elevated.

An animal with bilateral disease of the vestibular system will have neither a head tilt nor any spontaneous or positional nystagmus. Wide excursions of the head from side to side are frequently seen, and the animal will lack a physiological nystagmus. Animals with acute vestibular disease may additionally display signs of anorexia or vomiting associated with the dysequilibrium. Meclozine (25 mg orally q24h in dogs, 12.5 mg orally q24h in cats) may be helpful in treating this.

# **Lesion localization**

The presence of a head tilt and jerk nystagmus is indicative of a disturbance of the vestibular system (Figure 10.2). Further evaluation is necessary to determine whether the central or peripheral components of the vestibular system are affected.

The peripheral components include the sensory receptors for vestibular input located in the



Lesion localization for head tilt and nystagmus; the brainstem is highlighted. The peripheral section of the vestibular system originates in the petrous temporal bone and the central section resides in the brainstem and flocculonodular lobe of the cerebellum. Inset: A magnified schematic illustration of the middle and inner ear structures.

membranous labyrinth of the inner ear and the vestibular portion of cranial nerve VIII (vestibulocochlear nerve). These peripheral structures are encased within the petrous temporal bone.

 The central vestibular components include nuclei and pathways within the brainstem and cerebellum.

Animals with central vestibular disease typically have additional clinical signs reflective of brainstem involvement. These can include: deficits of cranial nerves V through XII; depression of consciousness due to disturbance of the ascending reticular activating system; and evidence of ipsilateral paresis or postural reaction deficits, due to involvement of the upper motor neuron pathways to the limbs. Nystagmus seen with central diseases can be horizontal, rotary or vertical and may change direction with different positions of the head. In contrast, animals with a peripheral disease will have a normal level of consciousness (although they may exhibit profound disorientation) and no evidence of weakness or postural reaction deficits.

Facial nerve deficits and Horner's syndrome can be seen with peripheral disease, due to the proximity of cranial nerve VII (facial nerve) and the sympathetic nerve to cranial nerve VIII in the area of the petrous temporal bone. Either a horizontal or rotary nystagmus is seen.

With both central and peripheral diseases, the head tilt, circling and any limb deficits typically occur ipsilateral to the lesion. The differentiation of central and peripheral vestibular disease based on clinical findings is summarized in Figure 10.3.

Clinical sign	Central vestibular disease	Peripheral vestibular disease
Paresis	Possible	No
Proprioceptive deficits	Possible	No
Consciousness	May be depressed, stuporous, comatose	Alert; may be disoriented
Cranial nerve deficits	Cranial nerves V–XII may be affected	Cranial nerve VII only
Horner's syndrome	Rare	Possible
Nystagmus	Horizontal, rotary or vertical, with fast phase in any direction; may change direction with changes in head position	Horizontal or rotary with fast phase away from side of the lesion; direction not altered with head position

10.3 Clinical findings associated with peripheral and central vestibular disease.

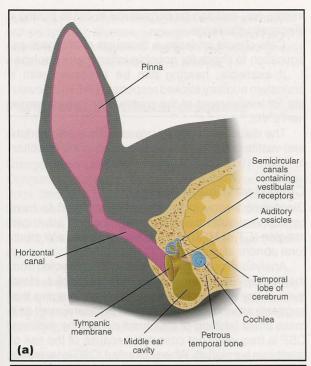
#### Paradoxical vestibular disease

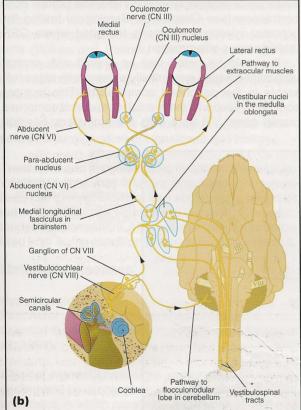
Vestibular signs can also be seen with cerebellar lesions that involve the flocculonodular lobe or the caudal cerebellar peduncle. This syndrome is called paradoxical vestibular disease because the head tilt and circling occur contralateral to the lesion. There is usually some evidence of cerebellar disease on neurological examination, such as ipsilateral dysmetria, a head tremor or a truncal sway. These lesions also often affect the proprioceptive and motor pathways in the region, resulting in postural reaction deficits ipsilateral to the lesion but contralateral to the head tilt. Chapter 12 contains further details on cerebellar disease.

# **Pathophysiology**

The vestibular system functions to maintain an animal's balance and orientation with respect to gravity. The system detects linear acceleration and rotational movement of the head, and is responsible for maintaining the position of the eyes, trunk and limbs in reference to the position of the head.

The sensory receptors for vestibular input are located in the membranous labyrinth of the inner ear (Figure 10.4). The saccule and utricle are primarily responsible for detecting gravity and linear acceleration, and the semicircular canals detect rotation. Input from the receptors enters the brain via the vestibular portion of cranial nerve VIII, where the majority of fibres terminate in one of four vestibular nuclei. The remaining axons terminate in the cerebellum. Pathways from the vestibular nuclei project to the nuclei of cranial nerves III (oculomotor), IV (trochlear) and VI (abdu-





(a) Schematic overview of the anatomy of the middle and inner ear. (b) Schematic overview of the neuronal connections that form the peripheral and central vestibular system. Stimulation of the peripheral vestibular system in the inner ear ultimately produces a conjugate deviation of the eyes to the ipsilateral side.

cent) to control eye movements, as well as to other brainstem centres and the cerebellum, cerebral cortex and spinal cord (Figure 10.4).

A head tilt results from the loss of anti-gravity

muscle tone on one side of the neck. Jerk nystagmus develops from the dysfunction of the pathways responsible for integrating vestibular input with the extraocular eye muscles. This results in a loss of coordinated eye movements when the head moves. The slow phase of the jerk nystagmus is the pathological phase, with the fast phase being corrective or compensatory.

Animals use sight and touch to compensate for stable or slowly progressing vestibular disease. This may explain the improvement that can be seen in many animals after the onset of vestibular signs, regardless of the underlying cause of the disease.

# **Differential diagnosis**

The differential diagnoses for an animal with vestibular disease vary considerably depending on whether the vestibular deficits are determined to be central or peripheral in origin.

The two most common disease processes that cause central vestibular signs are neoplasia and infection/inflammation, whilst the two most common diagnoses in animals with peripheral vestibular signs are otitis media/interna and idiopathic vestibular disease. A complete list of differential diagnoses for central and peripheral vestibular localizations is given in Figure 10.5.

Mechanism of disease	Central vestibular disease	Peripheral vestibular disease
Degenerative	Lysosomal storage disorders Neurodegenerative diseases [12]	
Anomalous	Chiari-like malformation [13,14]	Congenital vestibular disease [10]
Metabolic		Hypothyroidism [10]
Nutritional	Thiamine deficiency [10]	og Hilliam samme
Neoplasia	Brain tumours [8]	Tumours of middle or inner ear [10]
Inflammatory	Meningoencephalitis [10]	Otitis media/interna Nasopharyngeal polyps [10]
Idiopathic	Arachnoid cysts	Idiopathic vestibular disease [10]
Toxic	Metronidazole [10]	Aminoglycosides, topical iodophors, chlorhexidine others [10]
Trauma	Head trauma [19]	Trauma to middle or inner ear [10]
Vascular	Cerebrovascular disease	

Differential diagnoses associated with peripheral and central vestibular system disease. Numbers in square brackets refer to chapters where details can be found.

# **Neurodiagnostic investigation**

A thorough history should be obtained to gain information with respect to the onset and progression of the disease, any history of trauma, vaccination history, presence of other clinical signs, history of ear disease and whether potentially ototoxic drugs have been administered.

A complete neurological examination is necessary to determine whether the vestibular deficits are due to a central or a peripheral disease, which will then dictate the emphasis of further diagnostic testing. Complete blood count, blood chemistry, thyroid panel and urinalysis should be performed in all animals presenting with vestibular signs. This can be useful in identifying potential inflammatory or metabolic disturbances that may be responsible for the clinical signs, in addition to serving as a general health screen, as further diagnostic testing usually requires general anaesthesia.

# Peripheral vestibular disease

An animal determined to have peripheral vestibular disease should undergo a thorough otoscopic examination, performed under anaesthesia, along with radiographs of the tympanic bullae to assess for otitis media or interna (OM/OI). It should be noted that normal radiographs do not rule out OM/OI. If there is evidence of OM/OI, a sample of fluid should be obtained, via myringotomy, to submit for cytology and bacterial culture.

Computed tomography (CT) scan and magnetic resonance imaging (MRI) of the tympanic bullae are the most sensitive means of identifying fluid within the

middle ear, and can be considered in cases posing a diagnostic challenge.

Cats should undergo a thorough pharnygeal examination to check for possible inflammatory polyps.

If available, hearing can be assessed with a brainstem auditory evoked response (BAER), to evaluate for involvement of the cochlear branch of cranial nerve VIII.

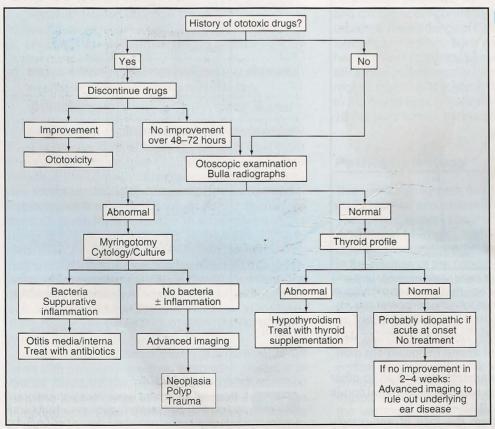
The diagnostic approach to an animal with peripheral vestibular disease is summarized in the flowchart in Figure 10.6.

# Central vestibular disease

Diagnostic testing in an animal determined to have central vestibular disease should include advanced imaging (CT or MRI) of the brain to identify any structural abnormalities.

Analysis of cerebrospinal fluid (CSF) collected from the cerebellomedullary cistern can be helpful. However, if any abnormality is identified on imaging that suggests an increased intracranial pressure, such as a mass effect (shifting of structures across the midline), CSF is frequently not collected because of the risk of fatal brain herniation. When collected, CSF is tested for evidence of inflammation and increased protein concentrations (see Chapter 3). Serological testing for potential infectious agents is indicated where CSF testing shows inflammation.

It should be noted that an animal with central vestibular disease may initially present with signs referable to the peripheral components. This is most commonly seen with extra-axial masses that compress cranial nerve VIII as it exits the brainstem. For this



Diagnostic algorithm for the work-up of an animal presenting with signs of peripheral vestibular disease.

reason, it is recommended that an animal with apparent peripheral disease undergo brain imaging and possible CSF analysis if signs do not improve with treatment over a course of 2–4 weeks.

# Peripheral vestibular diseases

## **Anomalous diseases**

# Congenital vestibular disease

Congenital vestibular diseases are seen infrequently in dogs and cats but have been reported in Siamese, Burmese and Tonkanese cats, and in Dobermann Pinschers, Cocker Spaniels, German Shepherd Dogs, Akitas, Smooth Fox Terriers and Beagles (see Appendix 1).

**Clinical signs:** The onset is usually first noticed between 3 and 12 weeks of age. Head tilt, ataxia and circling may be seen, and the animal may be deaf. Nystagmus is not a characteristic feature.

**Pathogenesis:** The pathogenesis is not known. One study of Dobermann Pinschers demonstrated non-inflammatory cochlear degeneration in affected animals, with progressive loss of the auditory sensory hair cells (Wilkes and Palmer, 1992), whilst a separate study revealed the presence of lymphocytic labyrinthitis in affected Dobermann Pinscher puppies (Forbes and Cooke, 1991).

**Diagnosis:** Diagnosis is by exclusion of other disorders and consideration of signalment and history.

**Treatment and prognosis:** No treatment is available. Vestibular signs may improve over time; this is most likely due to compensation for a static vestibular deficit rather than disease resolution. Deafness, if present, tends to be permanent. Affected animals should not be bred from as the condition is presumed to be inherited.

#### Metabolic diseases

#### Hypothyroidism

Peripheral vestibular disease has occasionally been reported in association with hypothyroidism (Jaggy *et al.*, 1994).

Clinical signs: Clinical signs include head tilt, ataxia, circling and positional strabismus, unless the disease is bilateral, in which case wide excursions of the head and neck result. Facial nerve paresis has been reported in conjunction with the vestibular signs in some dogs. Signs commonly attributed to hypothyroidism, such as lethargy, weight gain and poor hair coat, are frequently absent in affected dogs. Onset of signs can be either acute or chronic, and the disease course may be either progressive or non-progressive.

**Pathogenesis:** The pathogenesis of peripheral nerve disease associated with the hypothyroid state is not completely understood, although it is believed to reflect

a deficit in energy metabolism and resultant disturbance in axonal transport.

**Diagnosis:** Diagnosis is based on laboratory evaluation of thyroid function and response to treatment.

**Treatment and prognosis:** Supplementation with levothyroxine is the standard therapy. Resolution of most neurological deficits are expected within 2 months, although a residual head tilt and positional strabismus may persist.

# Neoplastic diseases

### Tumours of the middle or inner ear

Clinical signs: Neoplastic conditions of the inner or middle ear can cause peripheral vestibular signs in dogs and cats. Tumours that have been reported to cause vestibular disease include: fibrosarcoma, chondrosarcoma and osteosarcomas of the osseous bulla; squamous cell carcinoma; adenocarcinoma; and lymphoma (Kirpensteijn, 1993; Garosi et al., 2001).

**Pathogenesis:** Vestibular signs are caused by destruction or compression of cranial nerve VIII by the tumour.

*Diagnosis:* Radiographs of the skull often reveal destruction of the tympanic bulla; associated soft tissue swelling or periosteal reaction may also be evident. Advanced imaging via CT or MRI provides additional detail with respect to the origin and extent of the neoplastic process and determines whether the tumour has invaded the cranial vault (Figure 10.7).



## 10.7

CT scan of a cat with an aggressive tumour involving the right tympanic bulla. There is bony destruction of the bulla, extensive soft tissue involvement and evidence of extension into the cranial cavity.

**Treatment and prognosis:** Complete surgical resection of tumours involving the middle or inner ear is difficult. Adjunctive radiation therapy is recommended when complete surgical resection is not possible. Prognosis depends on the tumour type and extent of disease, but overall tends to be poor.

# Inflammatory diseases

# Otitis media/interna (OM/OI)

Otitis media/interna is one of the more commonly recognized causes of peripheral vestibular disease in both dogs and cats.

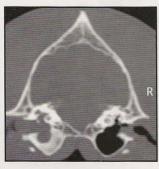
Clinical signs: Evidence of otitis externa may be apparent on general physical examination. Facial nerve paralysis and/or Horner's syndrome can be seen in association with the vestibular signs, due to the close association of cranial nerve VII and the sympathetic supply with the petrous temporal bone. Disease is most frequently unilateral, but bilateral disease can also occur.

**Pathogenesis:** OM/OI typically develops as an extension of otitis externa, with common bacterial isolates including *Staphylococcus intermedius* and *Pseudomonas* spp. (Cole *et al.*, 1998). OM/OI can occur in the absence of otitis externa, in which case it is believed to be due to ascent of bacteria from the oral cavity through the auditory tube or by haematogenous spread.

*Diagnosis:* Diagnosis is based on thorough otoscopic examination and imaging of the tympanic bullae. Radiographs of the tympanic bullae may reveal evidence of fluid density within, and sclerosis of, the bulla (Figure 10.8). However, radiographs may be normal in some cases, particularly early in the course of disease, and thus additional imaging techniques such as CT or MRI, may be required to provide more sensitive imaging of the bone and soft tissue in the affected area (Figure 10.9).



Open mouth bulla radiograph of a dog with unilateral otitis media/interna. The left tympanic bulla is obscured by bone and soft tissue density (arrowed) when compared with the normal air-filled right bulla.



CT scan of a dog with chronic left-sided otitis media/interna. Note the bony sclerosis and soft tissue density within the tympanic bulla.

Any exudate noted in the external ear canal should be removed by gentle saline irrigation to visualize the tympanic membrane. The tympanic membrane is frequently ruptured; if it is intact, it may appear to be bulging into the external ear canal.

If fluid is visualized within the middle ear, an attempt should be made to obtain a sample via myringotomy. This can be performed by inserting a 22-gauge spinal needle or tomcat catheter through the ventral aspect of the tympanic membrane, using an otoscope for guidance. The fluid present can then be gently aspirated into a syringe and submitted for cytology and bacterial culture.

Treatment and prognosis: Treatment for bacterial OM/OI consists of a 4–6 week course of systemic antibiotics. The clinician's choice of antibiotics should be based on the results of culture and sensitivity testing (if samples are successfully obtained via myringotomy). Otherwise, an antibiotic that is effective against the most common causative organisms and that will penetrate into the tympanic bullae should be chosen, e.g. amoxicillin/clavulanate, a cephalosporin or a fluoroquinolone.

Otic cleansing products should not be used, particularly if the tympanic membrane cannot be initially visualized. If cleansing products escape into the middle ear, they can worsen the vestibular signs and cause deafness.

Prognosis is good for resolution of the infection, although neurological deficits may persist after effective medical therapy due to irreversible damage to the neural structures. Cases that are unresponsive to medical therapy may require surgical drainage and debridement via bulla osteotomy. Occasionally, an infection can extend into the cranial vault causing central rather than peripheral vestibular signs to predominate (Figure 10.10). This may be more common in animals with OM/OI that have been treated with corticosteroids.



Contrastenhanced CT
scan of a dog with otitis
media/interna, with extension
into the brain. Note the soft
tissue density within the
tympanic bulla (arrowed).
The contrast medium has
enhanced areas at the
cerebellopontine medullary
angle on the same side
(arrowheads).

## Nasopharyngeal polyps

Nasopharyngeal (inflammatory) polyps are comprised of well vascularized fibrous tissue lined by epithelium.

Clinical signs: Disease is identified most frequently in cats from 1 to 5 years of age. Polyps may cause signs of upper respiratory disease and dysphagia in addition to peripheral vestibular dysfunction. Evidence of otitis externa is often present.

**Pathogenesis:** Nasopharyngeal polyps originate in the auditory tube or the lining of the tympanic cavity, and grow passively into the nasopharynx or middle ear of cats, and very rarely dogs. Otitis media/interna can be a complication of auditory tube obstruction by the polyp.

**Diagnosis:** Diagnosis is based on visualizing the polyp in the nasopharynx or external ear canal during a thorough pharyngeal and otoscopic examination performed under anaesthesia. Radiographs may reveal occlusion of the nasopharynx or sclerosis and soft tissue opacity within the tympanic bulla. Advanced imaging can provide additional information on the extent of soft tissue involvement associated with the polyp (Figure 10.11).



CT scan of a cat with an inflammatory polyp in the right ear canal and secondary otitis media/interna. Note the soft tissue density within the tympanic bulla characteristic of OM/OI (black arrow) as well as the soft tissue density polyp obscuring the horizontal ear canal (white arrow).

**Treatment and prognosis:** Treatment involves removal of the polyp. Many polyps are attached to the auditory tube by a narrow stalk of tissue and this can be successfully removed with simple traction. More extensive polyps may require surgical removal via ventral bulla osteotomy. Horner's syndrome is a common postoperative complication following ventral bulla osteotomy, but tends to be transient.

Overall prognosis is good. However, recurrence is possible, especially for polyps removed non-surgically.

# Idiopathic diseases

# Idiopathic vestibular disease

Idiopathic vestibular disease is a common cause of vestibular disturbance in both dogs and cats.

Clinical signs: These most commonly reflect unilateral involvement of the peripheral vestibular system and can be quite severe and acute at onset. Occasionally, bilateral disease is seen, especially in cats. In contrast with many of the other diseases affecting the peripheral vestibular system, facial paresis and Horner's syndrome are not features of idiopathic vestibular disease (Schunk and Averill, 1983; Burke et al., 1985).

**Pathogenesis:** Idiopathic vestibular disease is characterized by the acute or even peracute onset of non-progressive peripheral vestibular signs.

- The canine form typically, but not exclusively, affects older dogs and is also known as canine geriatric vestibular disease.
- The feline disease is seen in cats of all ages and is documented to be most common in spring to autumn months, especially in the north-eastern states of the USA (no such temporal association has been made in Europe).

The aetiology of these disorders has not been determined. However, it has recently been hypothesized that the feline disease in the USA may be caused by *Cuterebra* larval migration (Glass *et al.*, 1998).

**Diagnosis:** Diagnosis is based on the presence of compatible history and physical examination findings, and by exclusion of other causes of peripheral vestibular disease. Typically, improvement in clinical signs is seen within 2–3 days.

**Treatment and prognosis:** No treatment is recommended aside from supportive care, which consists of administering intravenous fluids to animals that are vomiting, and confining the animal to a well padded area in order to minimize self-trauma secondary to disorientation. Meclozine can be given to treat nausea.

Prognosis is good, as the condition resolves on its own within 2–4 weeks. A mild residual head tilt or ataxia may persist in some animals.

# **Toxic diseases**

# Ototoxicity

*Clinical signs:* Ototoxic agents can affect vestibular function, hearing or both.

**Pathogenesis:** The systemic administration of aminoglycoside antibiotics is most commonly associated with ototoxicity. Prolonged therapy for more than 2 weeks with high doses of drug are necessary to induce the changes in normal animals; however, animals with renal impairment are more susceptible to developing toxicity.

Of the aminoglycoside antibiotics, streptomycin is most often associated with damage to the vestibular system. Other agents can induce ototoxicity when used topically, the most notable of which are the iodophors and chlorhexidine. Due to the potential for ototoxicity, topical otic preparations should never be introduced into the ear when the tympanic membrane cannot be visualized or is determined to be ruptured.

**Diagnosis:** Diagnosis is based on the acute onset of compatible clinical signs in an animal that has recently been administered an ototoxic agent, in addition to exclusion of other causes. Deafness can be confirmed with BAER testing.

**Treatment and prognosis:** No definitive treatment is possible. Vestibular signs usually improve over time, due to resolution of the damage or compensatory mechanisms, but deafness tends to be permanent.

#### **Traumatic diseases**

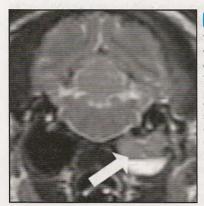
#### Trauma to the middle or inner ear

Clinical signs: Traumatic injuries to the middle and inner ear may result in peripheral vestibular signs. Horner's syndrome and facial nerve involvement may also be seen, due to the close association of these nerves to cranial nerve VIII in the area of the petrous temporal bone.

Facial abrasions and swelling may be apparent in some animals, and haemorrhage may be present in the external ear canal on the affected side.

**Pathogenesis:** Vestibular signs are caused by direct damage to cranial nerve VIII, or compression by bone fragments or haemorrhage.

**Diagnosis:** In addition to a suggested or confirmed history of trauma, radiographs may reveal fractures of the tympanic bulla. CT or MRI (Figure 10.12) can be helpful in showing fractures not identified on skull radiographs, as well as determining the extent of soft tissue involvement, respectively.



10.12

Transverse T2weighted MRI scan of a cat following a traumatic head injury causing acute clinical vestibular signs and middle ear haemorrhage (arrowed).

**Treatment and prognosis:** No specific treatment is typically recommended other than that required for the head trauma itself (Chapter 19).

Prognosis depends on the severity of the injury. In general, vestibular signs tend to improve over time, but residual deficits may persist.

# Central vestibular diseases

# **Degenerative diseases**

# Lysosomal storage disorders and neurodegenerative diseases

Lysosomal storage disorders are inborn errors of metabolism in which specific deficiencies of degradative enzymes cause substrate accumulation and result in cellular and clinical dysfunction.

Neurodegenerative disorders are diseases associated with an abnormality in the metabolic pathway that leads to early death of the neuron. Several of these conditions can present with ataxia and incoordination suggestive of vestibular disease. (See Chapter 12 for a more detailed discussion of this class of disorders and Appendix 1 for a list of reported breed associations.)

## **Anomalous diseases**

## Chiari-like malformations

Chiari-like malformations are congenital defects characterized by caudal displacement of part of the cerebellum through the foramen magnum. This occurs as a result of occipital bone dysplasia causing the caudal fossa to become abnormal in size or shape. This malformation can cause compression of the brainstem and cerebellum, and result in signs of central vestibular disease. A more thorough discussion of Chiari-like malformations can be found in Chapters 13 and 14.

# **Neoplastic diseases**

#### **Brain tumours**

Of the primary brain tumours seen in dogs, meningiomas and choroid plexus papillomas have a site predilection for the caudal fossa. As such, vestibular signs are commonly encountered in affected animals. The reader is referred to Chapter 8 for a more thorough discussion of brain tumours.

Dermoid and epidermoid cysts are occasionally classified as neoplastic abnormalities. Many of the canine epidermoid cysts reported have been located in the cerebello-pontine angle and can extend into the fourth ventricle (Platt et al., 1999). Although these cysts can be incidental findings on post-mortem examination, dogs with clinical signs consistently have vestibular dysfunction. The cysts have a stratified squamous epithelium lining and expand by progressive exfoliation into the lumen. Definitive treatment is achieved by total surgical removal of the cyst; however, success of surgical resection depends on the location of the lesion.

Intracranial dermoid cysts are rarer than epidermoid cysts in dogs. Dermoid cysts are neoplastic lesions with a complex cyst wall, containing both epidermoid tissue and adnexa. Due to the caudal fossa location of these lesions, they can be associated with vestibulo-cerebellar signs and obstructive hydrocephalus. Both types of cyst have characteristic MRI signs (Platt et al., 1999; Targett et al., 1999).

#### **Nutritional diseases**

# Thiamine deficiency

Although now not commonly encountered, a deficiency of thiamine (Vitamin B1) can cause a progressive encephalopathy in both dogs and cats.

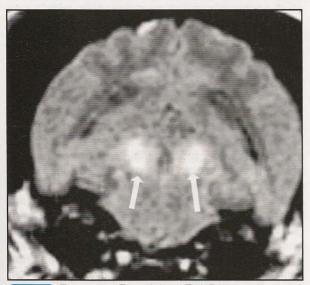
Clinical signs: Initial clinical signs include anorexia and lethargy. Neurological deficits develop a few days later, and commonly manifest as vestibular signs, along with pupillary dilation and seizures. As this is a bilaterally symmetrical disease, the vestibular signs often present as wide excursions of the head and neck with poor to absent physiological nystagmus.

Cats can develop marked ventroflexion of the head and neck and will curl up in a tight semicircular posture. Paraparesis can also be seen in dogs.

**Pathogenesis:** Thiamine plays an essential role as a coenzyme in the metabolism of carbohydrates. Inhibition of carbohydrate metabolism in a thiamine-deficient state leads to energy depletion and results in neuronal necrosis.

Thiamine deficiency in cats most frequently results from feeding a raw fish diet that is rich in thiaminase. Excessive amounts of cereal in the diet has also been shown to predispose cats to thiamine deficiency. Thiamine deficiency can be caused in dogs by feeding them cooked meat or canned food heated to excessive temperatures (>100°C). In addition, the use of sulphur dioxide as a preservative can destroy thiamine in food and cause signs of deficiency in both dogs and cats.

**Diagnosis:** Diagnosis is based on historical findings suggesting a thiamine-deficient diet (although this may not always be evident), along with compatible examination findings and exclusion of other causes. MRI may demonstrate the presence of bilaterally symmetrical areas of haemorrhage and malacia within susceptible nuclei of the brain (Garosi *et al.*, 2003) (Figure 10.13).



Transverse T2-weighted FLAIR magnetic resonance cerebral image of a dog with confirmed thiamine deficiency. The caudal colliculi on both sides are hyperintense, compatible with cytotoxic oedema of these nuclei (arrowed). (Courtesy of Laurent Garosi.)

Gross pathological findings include bilaterally symmetrical petechial haemorrhages in brainstem nuclei, with the caudal colliculi most frequently affected. Microscopic lesions are confined to the grey matter and are characterized by focal, symmetrical areas of oedema and neuronal necrosis.

**Treatment and prognosis:** The disease is rapidly progressive and typically fatal if left untreated. However, treatment with thiamine (12.5–50 mg/dog or 12.5–25 mg/cat i.m or s.c q24h until oral supplementation is possible) in the early stages of disease can lead to rapid reversal of clinical signs, although some signs, such as blindness and wide excursions of the head and neck, may be residual.

# Inflammatory diseases

# Meningoencephalitis

Meningoencephalitis refers to inflammation of the brain and surrounding meninges.

Clinical signs: As a general rule, inflammatory diseases tend to be acute at onset and progressive, with a multifocal or diffuse, often asymmetrical, distribution within the central nervous system (CNS). Neurological manifestations are quite variable and reflect the location of the inflammatory foci within the nervous system.

Central vestibular signs are commonly encountered, and may be seen alone or combined with other neurological signs. Neck pain may also be present as

a manifestation of meningeal inflammation. Animals with CNS infections frequently do not have evidence of systemic involvement. Therefore, the absence of fever, anorexia and depression, and the presence of a normal blood count cannot be used to exclude the possibility of an infectious aetiology in an animal with neurological signs.

**Pathogenesis:** Infectious causes of CNS inflammation in small animals include viral, protozoal, fungal, parasitic and bacterial organisms. The most commonly recognized CNS infections in dogs include:

- · Canine distemper virus
- Rickettsial disease (e.g. ehrlichiosis and Rocky Mountain spotted fever)
- Protozoal infections (e.g. toxoplasmosis and neosporosis)
- Fungal diseases (e.g. cryptococcosis).

Inflammatory, non-infectious causes of CNS dysfunction in dogs include such diseases as granulomatous meningoencephalomyelitis (GME) and necrotizing encephalitis.

CNS infections in cats most commonly involve feline infectious peritonitis (FIP), toxoplasmosis and cryptococcosis.

A detailed list of infectious causes of meningoencephalitis is given in Figure 10.14.

Diagnosis: A thorough ophthalmological examination should be performed in every neurological case to look for evidence of fundic changes or uveitis compatible with inflammatory disease. Definitive diagnosis of CNS inflammatory disease is typically based on finding an increase in white blood cell (WBC) numbers or an abnormal cell type distribution, with a concomitant increase in protein concentrations, on CSF analysis (see Chapter 3). In rare instances, normal CSF can be obtained from an animal with confirmed CNS inflammatory disease. This can occur if the inflammation does not involve the meninges or the ependymal lining of the ventricular system or if the animal has been treated with corticosteroids prior to CSF collection. Elevations in protein concentration can result from breakdown of the blood-brain barrier or intrathecal antibody production. It is likely that both of these mechanisms contribute to the elevated protein levels recognized with most CNS inflammatory disease.

Cytological evaluation of the fluid provides additional information as to possible causes:

- Viral diseases typically result in mild lymphocytic inflammation, an exception to this is FIP, which can cause a neutrophilic pleocytosis
- Bacterial infections usually cause a marked increase in neutrophils in the CSF, with cell counts often >500 cells/μl. There is also evidence of toxic changes in cell morphology. However, mixed neutrophilic and mononuclear inflammation may be observed in animals with bacterial diseases that have been previously treated with antibiotics

## Viral

Canine distemper

Rabies

Pseudorabies

Canine herpesvirus

Canine parainfluenza

Canine parvovirus

Infectious canine hepatitis

Central European tick-borne encephalitis

Borna disease virus

Feline infectious peritonitis

Feline immunodeficiency virus

Feline leukaemia virus

#### Protozoal

Toxoplasmosis

Neosporosis

Encephalitozoonosis

Acanthamoebiasis

Sarcocystis-like organism

Trypanosomiasis

Babesiosis

### Rickettsial

Ehrlichiosis

Rocky Mountain spotted fever

Salmon poisoning disease

#### Bacterial

Aerobes

Anaerobes

Leptospirosis

# Fungal

Cryptococcosis

Blastomycosis

Histoplasmosis

Coccidioidomycosis Aspergillosis

Phaeohyphomycosis

Hyalohyphomycosis

#### **Parasitic**

Cuterebra

Dirofilaria immitis

Toxocara canis

Ancyclostoma caninum

Angiostrongylus cantonensis

# Algal

Protothecosis

## Idiopathic

Granulomatous meningoencephalomyelitis

Necrotizing meningoencephalomyelitis

Polioencephalomyelitis

Pyogranulomatous meningoencephalomyelitis

Eosinophilic meningoencephalitis

Periventricular encephalitis

Examples of infectious diseases and organisms responsible for clinical meningoencephalitis in dogs and cats.

- Rickettsial infections frequently cause mild mononuclear inflammation, although neutrophilic inflammation can be seen with Rocky Mountain spotted fever, secondary to an associated vasculitis
- Protozoal diseases most often result in mild to moderate inflammation, with a mixed population of neutrophils and mononuclear cells, with occasional eosinophils
- Fungal infections usually cause a mixed or primary neutrophilic inflammation. Eosinophils may also be seen, especially with cryptococcosis.

Additional testing, based on the cytological evaluation, is performed in an attempt to identify an infectious cause for the inflammation. These tests can include: culturing the CSF for bacterial or fungal organisms; measuring serum and CSF antibody or antigen titres; and CSF polymerase chain reaction (PCR) analysis if available. However, despite extensive testing, an underlying cause for the inflammation is not discovered in most cases.

Treatment and prognosis: Treatment is aimed at the primary disease process. Treatment with clindamycin (10 mg/kg orally q12h) and/or trimethoprim/sulphonamide (15 mg/kg orally q12h) for potential protozoal infections may be initiated once a diagnosis of encephalomyelitis has been made based on CSF results, while additional test results are pending. If no infectious cause is discovered upon additional testing, or the animal does not respond to initial antibiotic therapy, treatment with corticosteroids is initiated. Anti-inflammatory doses are often effective in alleviating clinical signs but higher, immunosuppressive doses may be required in some instances to appropriately manage immune-mediated disease.

Prognosis is variable and dependent on both the cause of the inflammation and the extent and severity of associated neurological deficits. Some infections, especially those caused by protozoal and fungal agents, are difficult to eradicate and relapses are common. In addition, residual neurological deficits may persist despite successful treatment of an infection due to irreversible damage caused by the inciting agent.

# **Bacterial encephalitis**

Bacterial infection is a relatively rare cause of encephalitis in dogs and cats when compared with other species.

*Clinical signs*: Animals can exhibit a variety of signs of intracranial disease including: vestibular dysfunction; seizures; cerebellar signs; paresis; cervical hyperaesthesia and coma (Radaelli and Platt, 2002). Fever is present in approximately 50% of cases at presentation. The signs are usually rapidly progressive and frequently fatal.

**Pathogenesis:** Bacterial infection of the brain is usually a consequence of direct extension of infection from the middle ear or sinuses (Spangler and Dewey, 2000) or a penetrating injury to the skull (surgical or

traumatic). Haematogenous spread can occur less commonly. Both aerobic and anaerobic infections have been reported. It is possible for the infection to be limited to the extradural or subarachnoid space, especially following bite wounds, in which case the infection may remain localized (intracranial empyema or abscess) and signs may not be so rapidly progressive. Clinical signs are largely the result of the inflammatory reaction that bacteria incite.

Diagnosis: Routine blood work will usually reflect an inflammatory process, but can be normal. A urine sample should be cultured if bacterial encephalitis is suspected, and blood cultures may be indicated in animals in which there is no obvious source of infection. Imaging of the brain (CT or MRI) is helpful to identify defects in the skull and OM/OI and may be suggestive of an inflammatory process. CSF analysis is the most useful test. Typically there is a marked elevation in the protein level and WBC count and the majority of cells are degenerate neutrophils. Bacteria may be visible in the spinal fluid. However, CSF can be unremarkable or may show more non-specific inflammatory changes. CSF should be cultured if it contains degenerate neutrophils, although it is common for cultures to be negative (Radaelli and Platt, 2002). Samples for culture should be obtained from the middle ear by myringotomy if OM/OI is present.

Treatment and prognosis: While the results of the culture are pending, treatment with an antibiotic that will penetrate the CNS should be initiated (see Chapter 21). The most common bacterial isolates are Escherichia coli, Streptococcus and Klebsiella, but anaerobic infections can also occur. Appropriate antibiotics include enrofloxacin and third generation cephalosporins. Many patients are in a critical condition and may need intravenous fluids and anti-inflammatory drugs. Mechanical ventilation may be necessary in comatose patients. Prognosis is poor in animals with rapidly progressing severe signs. Early appropriate treatment is vital to obtain a good outcome.

## Canine distemper virus infection

Canine distemper virus (CDV) is a paramyxovirus that commonly infects the CNS of dogs.

## Clinical signs:

- Neurological signs include: seizures; visual deficits; vestibular dysfunction; cerebellar signs; paresis; and myoclonus. The presence of myoclonus is most commonly associated with CDV infection but is not pathognomonic as it has been described in other inflammatory CNS disorders. Neurological disease associated with CDV infection tends to have a progressive course. Disease can develop in well vaccinated animals, so previous vaccination history does not exclude the possibility of CDV-associated disease.
- Systemic signs of disease, such as respiratory and gastrointestinal involvement, are reported to precede the neurological signs by 2–3 weeks.

- However, many dogs have no previous history of disease prior to the onset of neurological signs.
- Extraneural signs of disease include: conjunctivitis; rhinitis; fever; respiratory signs; gastrointestinal signs; tonsillitis; cachexia; enamel hypoplasia; and hyperkeratosis of the footpads or nose. These signs are frequently mild (Tipold et al., 1992; Koutinas et al., 2002).
- Fundic examination is recommended in all suspected cases, as many dogs have evidence of chorioretinitis.

Pathogenesis: The presence and severity of neurological signs is dependent on such factors as the age and immunocompetence of the host and the neurovirulence of the virus strain. Many dogs probably develop transient CNS infections without concurrent clinical signs. In the CNS, CDV initially replicates in neurons and glial cells, and can cause both grey and white matter lesions, with one usually predominating. These early degenerative lesions are not characteristically inflammatory. A chronic course of CNS infection results from a late or insufficient immune response to CDV, with characteristic inflammatory demyelinating lesions (Tipold et al., 1992). Polioencephalomyelopathy (PEM) has been reported most frequently in immature dogs, while leucoencephalomyelopathy (LEM) or a combination of PEM and LEM is more common in mature animals (Thomas et al., 1993).

**Diagnosis:** An indirect fluorescent antibody test for viral antigen in conjunctival smears can be positive in many dogs with CNS distemper, regardless of whether the disease is acute or chronic (Thomas *et al.*, 1993). Viral antigen may also be demonstrated in tracheal washings and urine sediment.

CSF analysis is often the most helpful diagnostic test. However, during the acute stage of disease, inflammatory response is lacking and thus cell count and protein level may be normal. In the chronic stage of disease, a mononuclear pleocytosis is more frequently identified. An elevated CSF titre of antibody against CDV relative to the serum titre is supportive of a diagnosis.

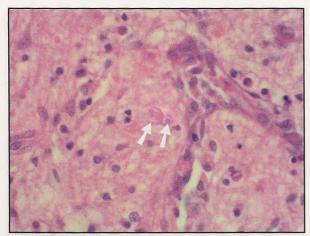
PCR analysis of serum and CSF for CDV is available in some laboratories.

MRI may demonstrate multifocal contrast-enhancing white or grey matter lesions (Figure 10.15).

Histopathology can confirm the presence of acidophilic intracytoplasmic or intranuclear inclusion bodies within neurons and occasionally astroglia (Figure 10.16).



Transverse T1-weighted contrast-enhanced MR image of a dog, demonstrating hyperintense lesions in the region of the vestibular nuclei in the medulla oblongata, due to distemper virus infection. (Courtesy of Laurent Garosi.)



A histopathological section of the area of the medulla affected in Figure 10.15. Arrows indicate intracytoplasmic acidophilic distemper viral inclusion bodies (H&E; original magnification X100). (Courtesy of Mark Bestbier and Laurent Garosi.)

**Treatment and prognosis:** There is no specific treatment for CDV-associated neurological disease. Overall, prognosis is poor, especially in cases with rapidly progressive signs. Seizures are reported to be an unfavourable prognostic sign as they are often difficult to control with antiepileptic drugs (Tipold *et al.*, 1992). However, the disease is not fatal in all instances, and some animals will recover.

Consequently, in cases where the neurological signs are not severe, it is recommended that the animal be administered supportive care and the disease progression monitored over 1–2 weeks before considering euthanasia (Tipold *et al.*, 1992).

# Feline infectious peritonitis

FIP, a coronavirus-induced disease, is a common cause of meningoencephalitis in cats.

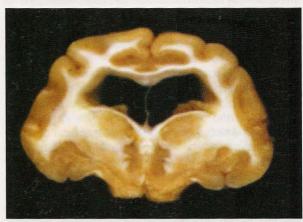
# Clinical signs:

- Neurological signs may include: seizures; cerebellar signs; vestibular dysfunction; and paresis. The disease often has an insidious onset, and may lack distinct clinical signs.
- Affected cats may have concurrent systemic signs, including anorexia and weight loss.
- Ocular lesions may also be identified, including: anterior uveitis; iritis; keratic precipitates; retinitis; and anisocoria.

**Pathogenesis:** The disease occurs most commonly in cats <3 years old and from multiple cat households (Foley *et al.*, 1998); however, cats as old as 15 years have been diagnosed with the disease (Kline *et al.*, 1994).

Neurological involvement is most common with the non-effusive or 'dry' form of the disease. Up to one-third of cats with the non-effusive form of the disease have been reported to have either primary neurological FIP or neurological signs as part of their overall disease presentation (Foley *et al.*, 1998). The FIP virus induces a pyogranulomatous and immune complex-mediated

vasculitis involving the meninges, ependymal lining, periventricular brain tissue and choroid plexus of the CNS. Secondary hydrocephalus can be seen due to obstruction of the ventricular system by the inflammation (Figure 10.17).

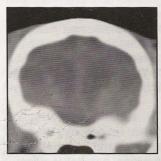


Pathological specimen from a cat with CNS FIP, demonstrating the marked dilation of the lateral ventricles that is often seen with the disease secondary to obstruction of the ventricular system.

**Diagnosis:** Haematological findings may include: anaemia; leucocytosis and hyperglobulinaemia; however, no abnormalities are present in some affected cats.

Serum tests for anti-coronavirus antibodies are often positive but have low specificity; however, a negative serum titre (i.e. a complete absence of antibody) does not exclude the possibility of FIP-associated neurological disease because soluble antibodies can form immune complexes and escape detection by standard tests.

Advanced imaging of the brain may reveal the presence of ventricular dilation (Figure 10.18). Periventricular contrast enhancement may be visible with MRI.



CT scan of a cat with CNS FIP, showing evidence of dilated lateral ventricles.

CSF analysis will show variable results. The characteristic finding is of a marked neutrophilic to pyogranulomatous pleocytosis, with cell counts often in the hundreds, and an associated increase in protein concentration to >200 mg/dl (Rand *et al.*, 1994). However, CSF may be normal, show mild mononuclear pleocytosis or have a normal cell count with an elevated protein concentration. Positive CSF titres have been shown to be the most useful ante-mortem indicator of neurological disease. However, positive antibody titres must be interpreted with respect to the integrity of the blood—brain barrier.

PCR assays performed on CSF have not been shown to be a reliable test for confirming disease (Foley *et al.*, 1998).

**Treatment and prognosis:** Prognosis for cats with CNS FIP is poor. Definitive treatment is not available. The use of immunosuppressive drugs may slow the progression of disease. Affected animals should be isolated from other cats to prevent the spread of infection.

## Toxoplasmosis and neosporosis

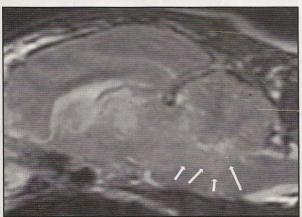
Toxoplasma gondii is an intracellular protozoan parasite of humans and animals that can cause encephalitis in infected dogs and cats. Neospora caninum is a more recently recognized protozoan parasite that is known to cause neurological disease in dogs but not cats.

**Clinical signs:** Signs of disease are seen most frequently in young or immunocompromised animals, and can occur with concurrent CDV infection or FIP.

- Neurological signs that have been reported with protozoan infections include: seizures; behavioural changes; cranial nerve deficits; cerebellar signs; and diffuse neuromuscular disease.
- A characteristic early sign of the disease is progressive rigidity of one or more limbs as a result of myositis and neuritis.
- Concurrent ocular abnormalities may be identified on fundoscopic examination.

**Pathogenesis:** Ingestion of tissue from infected intermediate hosts is the most common cause of *Toxoplasma gondii* infection in dogs and cats. In the case of *Neospora*, dogs are commonly infected *in utero*, although they can also be infected by ingestion of intermediate host tissue.

**Diagnosis:** Imaging may reveal the presence of either solitary or multiple mass lesions in the brain of affected animals (Figure 10.19).



10.19 A sagittal T2-weighted cerebral MR image of a cat that presented with vestibular disease due to CNS toxoplasmosis. Arrows indicate a diffuse area of hyperintensity associated with the infection within the brainstem, extending caudally to the area of the vestibular nuclei.

CSF analysis typically demonstrates pleocytosis with a mixed population of neutrophils and the presence of small and large mononuclear cells. Eosinophils may also be seen. With toxoplasmosis, a presumptive diagnosis is based on positive antibody titres in the CSF. However, a positive titre can be seen in animals previously exposed to the organism following non-specific immune stimulation and therefore is not definitive evidence of active disease (Lappin, et al., 1996). Serum and CSF anti-Neospora antibody titres are more reliable than serum titres alone. However, for both infections, evidence of a rising titre should be obtained.

Treatment and prognosis: Clindamycin and/or trimethoprim/sulphonamide (TMS) therapy is recommended in animals with CNS protozoal infections for a duration of 3–4 weeks. TMS can be combined with pyrimethamine (0.5–1 mg/kg q24h for 2 days then 0.25 mg/kg q24h for 2 weeks) and a folic acid supplement (5 mg/day) once the diagnosis has been confirmed. Neurological signs typically improve with treatment but may not resolve because of permanent damage caused by the organism. In addition, relapses are possible.

## Cryptococcosis

*Cryptococcus neoformans* is a saprophytic yeast with a worldwide distribution. The organism can be isolated from several sources, although its main reservoir is pigeon droppings.

*Clinical signs:* Many affected animals have non-specific signs: anorexia; weight loss; lethargy; lymphadenopathy; and pyrexia.

- Respiratory signs such as nasal discharge, sneezing or coughing may also be seen, as well as skin lesions.
- Ocular disease is often seen in association with neurological signs, and includes: anterior uveitis; chorioretinitis; and retinal detachment.
- Neurological signs include forebrain signs (e.g. seizures, behaviour change, altered mentation, circling, head pressing, blindness) in addition to vestibular signs, cranial nerve deficits and paresis (Berthelin et al., 1994a; Gerds-Grogan and Dayrell-Hart, 1997).

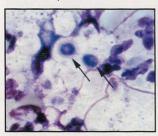
**Pathogenesis:** Dogs and cats most frequently become infected following inhalation of the organism. Neurological involvement results from haematogenous spread or local extension of an infection through the cribriform plate.

*Diagnosis:* The complete blood count may reveal the presence of monocytosis. In animals with extraneural disease, a definitive diagnosis can often be made based on cytology and/or culture of urine, nasal discharge, lymph node aspirates or cutaneous masses (Figure 10.20). In addition, these animals often have positive titres of cryptococcal capsular antigen.

Diagnosis of CNS cryptococcosis can often be made by cytological evaluation of CSF. Neutrophilic,

mononuclear or mixed pleocytosis may be seen, and eosinophils are frequently present. The encapsulated organism can be seen in cytological preparations in the majority of cases (Berthelin *et al.*, 1994b). The use of India ink, new methylene blue or Gram's stain allows the organism to be identified more readily.

In cases in which the organism is not observed on cytology, diagnosis can be made either by detecting cryptococcal capsular antigen in CSF or by culturing CSF samples.



Impression smear from a cat with cryptococcosis, demonstrating the presence of several encapsulated cryptococcal organisms (arrowed). (Diff-Quik; original magnification X500.)

**Treatment and prognosis:** Treatment with fluconazole or itraconazole is recommended, although overall prognosis is fair to poor. Non-steroidal anti-inflammatory drugs should be administered when antifungal therapy is initiated, to counteract the intense inflammatory reaction that accompanies the killing of *Cryptococcus*.

Long-term treatment is required, ranging from several months to years. It is difficult to rid the body completely of the organism and relapses are common. Treatment should be continued until serum cryptococcal titres are negative, or for 2 months beyond resolution of clinical signs.

## Granulomatous meningoencephalomyelitis

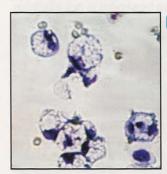
Granulomatous meningoencephalomyelitis (GME) is an inflammatory disease, of unknown aetiology, of the CNS of dogs and, less frequently, cats.

Clinical signs and pathogenesis: The disease is most common in middle-aged toy and small-breed dogs, with a possible breed predisposition in poodles and terriers. Three clinicopathological forms of the disease exist:

- The ocular form of the disease manifests with acute onset of dilated, unresponsive pupils due to optic neuritis
- The focal form of the disease presents with clinical signs suggestive of a single spaceoccupying mass, with areas of predilection in the pontomedullary region and forebrain
- The diffuse form of the disease presents with clinical signs suggestive of a multifocal CNS disorder, with the cerebrum, brainstem, cerebellum and cervical spinal cord most commonly involved. Clinical signs are usually acute in onset and progressive.

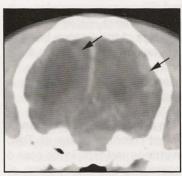
Although the cause of GME is unknown, characteristics of the lesion suggest a possible immunological basis for the disease (Vandevelde *et al.*, 1981). Infectious, autoimmune and neoplastic causes have all been proposed.

*Diagnosis:* CSF analysis typically reveals a mononuclear pleocytosis, with an associated increase in protein concentration (Figure 10.21). However, both neutrophilic pleocytosis and normal CSF analysis have been reported (Bailey and Higgins, 1986).



CSF sample from a dog with GME, demonstrating a predominance of large activated macrophages. (Diff- Quik; original magnification X500.)

A mass lesion may be evident on brain imaging with the focal form of the disease, while the brain parenchyma may have a patchy, heterogenous appearance with the diffuse form (Figure 10.22). Definitive diagnosis can only be made histologically on post-mortem examination or by biopsy. Ante-mortem diagnosis is usually presumptive, by exclusion of infectious aetiologies.



Contrastenhanced
CT scan of a dog with
disseminated GME,
demonstrating patchy
areas of contrast
enhancement
(arrowed). These
findings suggest
encephalitis of any
cause.

**Treatment and prognosis:** The most commonly prescribed treatment for GME consists of immunosuppressive doses of corticosteroids.

Other immunomodulatory drugs have also been utilized, e.g. cytarabine (cytosine arabinoside) and procarbazine (Cuddon and Coates, 2002). Cytarabine is administered at 50 mg/m²s.c. q12h for 2 consecutive days every 3 weeks. Procarbazine has been recommended at a dose of 25–50 mg/m² orally q24h, with an attempt to reduce the dose to every other day after one month of treatment. Both of these drugs are myelosuppressive, and complete blood counts should be monitored regularly during the course of therapy.

In addition, radiation therapy has been recommended as a treatment for dogs with the focal form of the disease (Muñana and Luttgen, 1998).

Overall, the prognosis is poor, but survival times range from weeks to years. The diffuse form of the disease carries the worst prognosis with a survival time of weeks to months (Muñana and Luttgen, 1998).

# Necrotizing meningoencephalomyelitis

Necrotizing meningoencephalomyelitis is a chronic progressive neurological disorder reported in Pugs (Pug encephalitis), Yorkshire Terriers and Maltese

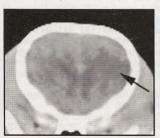
dogs. There are also sporadic reports of similar findings in other small-breed dogs, such as Shih Tzus.

# Clinical signs:

- Pug encephalitis is most commonly seen in juvenile to young adults, and causes seizures and other signs of forebrain dysfunction (Cordy and Holliday, 1989).
- The disease described in Maltese dogs also has a predilection for the forebrain (Stalis et al., 1995).
- The disease in Yorkshire Terriers causes signs of forebrain and brainstem involvement (Tipold et al., 1993).

**Pathogenesis:** The aetiology of the disease is unknown. Infection with an alpha-type herpesvirus has been suggested, based on histological similarities with this type of infection in humans. However, attempts at viral isolation have been unsuccessful. The disease is associated with necrosis and a non-suppurative meningoencephalitis predominantly in the cortex. The subcortical white matter is frequently involved.

**Diagnosis:** CT may reveal a focal hypodense area within the brain parenchyma relating to the area of necrosis (Figure 10.23). Areas of high signal intensityin the brain may be seen on MRI, usually within the white matter (Figure 10.24).



10.23 CT scan of a Yorkshire Terrier diagnosed with necrotizing encephalomyelitis, demonstrating a focal area of hypoattenuation in the right forebrain.



A transverse T2-weighted cerebral MRI image of a Maltese dog with necrotizing encephalitis demonstrating diffuse asymmetrical hyperintensity throughout the frontal lobe parenchyma (arrowed).

A lymphocytic pleocytosis is most frequently recognized on CSF analysis.

Definitive diagnosis is based on histopathology.

**Treatment and prognosis:** Prognosis is poor; no treatment is available, and the disease is typically fatal.

# Idiopathic diseases

#### **Arachnoid cysts**

Intracranial arachnoid cysts are rare but have been described most commonly in small brachycephalic

breeds of dog. These cysts have not been reported in cats to date, but probably do occur. Arachnoid cysts are accumulations of CSF that occur between two layers of the arachnoid membrane covering the neural parenchyma. These cysts can occur in any location along the CSF pathway, but in dogs are most commonly reported in the quadrigeminal cistern, a triangular space between the caudal cerebral hemispheres, dorsal to the midbrain and rostral to the cerebellum (Vernau *et al.*, 1997).

**Clinical signs:** Physical examination may reveal evidence of a domed calvarium and a persistent bregmatic fontanelle, as is characteristically seen with hydrocephalus.

Neurological findings in animals with quadrigeminal arachnoid cysts may include vestibular signs such as head tilt, ataxia and circling. Hemiparesis and depression may be apparent due to brainstem involvement.

Many dogs have clinical signs referable to a forebrain lesion including: seizures; visual deficits; and dementia. In these dogs, the cysts may be an incidental finding. Forebrain signs may occur alone, or, in combination with vestibular signs.

**Pathogenesis:** The cause of these cysts is not known, but in most cases it is believed to be congenital and reflects splitting of the arachnoid mater.

*Diagnosis:* Diagnosis is based on brain imaging. Both MRI and CT characteristics have been described in dogs (Vernau *et al.*, 1997). The cysts are in the typical extra-axial location, have sharply delineated margins and contain a fluid that is either isodense or isointense compared with CSF (Figure 10.25). The cyst wall and contents are not enhanced by intravenous administration of contrast media.

Arachnoid cysts of the quadrigeminal cistern can also be identified using ultrasonography, with images obtained through a persistent bregmatic fontanelle, the temporal window in the area of thin bone at the junction of the temporal and parietal bone, or the foramen magnum (Saito et al., 2001). The majority of affected animals have enlarged lateral ventricles in addition to the fluid-filled cyst at the level of the quadrigeminal cistern (see Figure 10.25). CSF should be collected to rule out the possibility of underlying infectious or inflammatory diseases.



CT scan of a dog with an intracranial cyst in the region of the quadrigeminal cistern. The cistern is represented by the sharply delineated, triangular fluid-filled space (arrowed). Note the dilated lateral ventricles either side.

**Treatment and prognosis:** Reports on treatment for intracranial arachnoid cysts in dogs are limited. Medical management consists of administering antiepileptic

drugs to animals with seizures, and prednisolone to decrease CSF production.

Surgical management has been described in a few dogs and consists of either fenestrating or shunting the cyst (Vernau *et al.*, 1997). Information on long-term follow-up is not available for dogs treated either medically or surgically, and consequently overall prognosis is unknown.

# **Toxic diseases**

# Metronidazole toxicity

*Clinical signs:* Central vestibular signs have been reported in dogs after administration of metronidazole (Dow *et al.*, 1989; Evans *et al.*, 2003).

Initial clinical signs are anorexia and vomiting, which can progress rapidly to include bilateral central vestibular signs with either a symmetrical or asymmetrical generalized ataxia and a positional vertical nystagmus. Head tilt and seizures are observed less frequently.

Onset of clinical signs can occur as soon as 3 days after initiating treatment but can also be seen after chronic therapy. Dogs reported to have developed toxicity were typically treated with an oral dose of metronidazole >60 mg/kg/day (Dow *et al.*, 1989), although doses as low as 30 mg/kg/day have been incriminated (Evans *et al.*, 2003).

Metronidazole toxicity has also been reported in cats, but affected cats display signs of forebrain and cerebellar involvement rather than vestibular signs (Saxon and Magne, 1993). Toxicity can be seen with lower doses than those reported for dogs.

**Pathogenesis:** The pathogenesis is poorly understood, but it is hypothesized to be related to interaction of metronidazole with the gamma-aminobutyric acid receptors in the cerebellum and vestibular nuclei (Evans et al., 2003).

**Diagnosis:** A history of metronidazole administration and compatible clinical signs should lead to a high suspicion for this disorder.

**Treatment and prognosis:** Treatment consists of discontinuation of the drug and provision of nursing care. In addition, administration of diazepam has been shown to shorten recovery times in dogs (Evans *et al.*, 2003). An intravenous injection of diazepam (0.43 mg/kg), followed by 0.43 mg/kg orally every 8 hours for 3 days, has been recommended.

Recovery is typically seen within 1–3 days in dogs treated with diazepam, and within 2–3 weeks for dogs in which treatment only consists of drug discontinuation and supportive care.

As is the case with dogs, signs in cats are reversible with discontinuation of the drug.

## **Traumatic diseases**

# Head trauma

Head trauma in dogs and cats is most often caused by automobile accidents, and injury to the brainstem can

result in vestibular signs along with other signs of brainstem dysfunction. (See Chapter 19 for details on the management of brain trauma.)

## Vascular diseases

#### Cerebrovascular disease

Cerebrovascular disease is being reported more frequently in dogs and cats with the greater availability of MRI as a diagnostic tool. A recent review of cerebellar infarcts in dogs and cats found the majority of animals to have a vestibular component to the neurological signs, either in the form of paradoxical vestibular disease or cerebellovestibular signs (Berg, 2003). The reader is referred to Chapter 8 for a more thorough review of cerebrovascular disease.

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# Neurological abnormalities of the head and face

# **Nick Jeffery**

# Introduction

Recognition of neurological abnormalities of the head and face plays a key role in identifying the distribution of a neurological disease and thereby suggesting possible aetiologies. Because of the large number of neural structures involved in causing such deficits (Figure 11.1) many of the conditions affecting the head and face will be described in greater detail in separate

chapters. Thus, vestibular dysfunction is covered in detail in Chapter 10 and ocular disorders are considered in Chapter 9. Since signs of cranial nerve dysfunction may result from both central nervous system (CNS) or peripheral nervous system (PNS) disorders a key component of diagnosis of neurological abnormalities of the head and face is to find evidence suggestive of either central or peripheral disease (generalized PNS disorders are covered in Chapter 14).



1.1 Schematic overview of cranial nerve origins and distribution in the dog.

# **Anatomy and clinical signs**

#### **Anosmia**

The olfactory portion of the rhinencephalon is the special visceral afferent system designed for the conscious perception of smell. The chemoreceptor is located in the olfactory epithelium of the caudal nasal mucosa. The axon leaving the cell body joins with other axons to form cranial nerve (CN) I (olfactory nerve). These nerves pass through the cribriform plate into the olfactory bulbs. Axons from the olfactory bulbs project through the olfactory tract to the ipsilateral olfactory cortex over the pyriform lobe.

Loss of sense of smell is difficult to ascertain clinically because of the lack of widely available objective testing methods, and is often due to abnormalities of the nasal cavity rather than specific neurological abnormalities. Depressed appetite and, perhaps, changed patterns of behaviour might be predicted consequences of anosmia. However, even in animals in which reduced sense of smell would be expected (those with large nasal tumours or aspergillosis) such signs are often not apparent.

#### External ophthalmoplegia

External ophthalmoplegia (paralysis of the extraocular muscles) causes strabismus and deficiencies in eye movements in specific directions due to dysfunction of CN III (oculomotor nerve), IV (trochlear nerve) and VI (abducent nerve) – these clinical signs are discussed in more detail in Chapter 9. It is important to differentiate disorders of specific extraocular eye muscles from vestibular lesions (see Chapter 10) as both can cause strabismus.

# Reduced facial and head sensation

11.2

Sensation to the head and face is provided by the three branches of CNV (trigeminal nerve): mandibular (cheek, lower teeth, tongue); maxillary (most of the face, cheek, side of nose and lateral eyelids); and ophthalmic (orbit, medial part of upper eyelid, dorsum of nose) (Figure 11.2). Therefore a lesion affecting the trigeminal nerve may, depending on its site, cause decreased sensation in any or all of these regions of the head. Decreased,

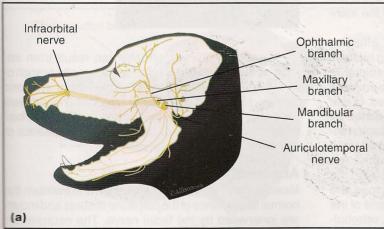
or loss of, facial sensation may also cause dysphagia due to poor prehension of food and water but is not commonly seen. The pinna of the dog is innervated by the facial nerve on the concave surface and by branches of the second cervical nerve on the convex surface, not by the trigeminal nerve.

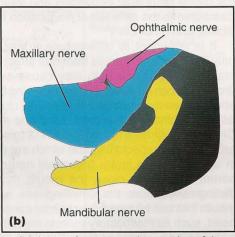
The cell bodies of the trigeminal sensory neurons are located in the trigeminal ganglia. The trigeminal sensory axons enter the pons just rostral to the origin of the facial and vestibulocochlear nerves and course caudally through the medulla in the spinal tract of the trigeminal nerve. This tract continues caudally into the first cervical segment. Lesions in the medulla involving the spinal tract of the trigeminal nerve result in ipsilateral loss of facial sensation but no impairment of masticatory muscle function. Lesions of the sensory cortex frequently cause subtle reductions in contralateral facial sensation, which can be most easily detected by touching the nasal mucosa using a small pair of forceps. Such subtle loss of function should be differentiated from the more gross loss of function caused by lesions of the trigeminal nerve.

The mandibular branch of CN V also provides motor innervation to the muscles of mastication. Sensory deficits, including diminished corneal and palpebral reflexes (Figure 11.3) may, therefore, occur in isolation or in conjunction with motor deficits, such as decreased jaw tone and/or loss of masticatory muscle bulk. Loss of sensory input from the cornea can result in 'neurogenic keratopathy' (this is discussed in greater detail in Chapter 9).

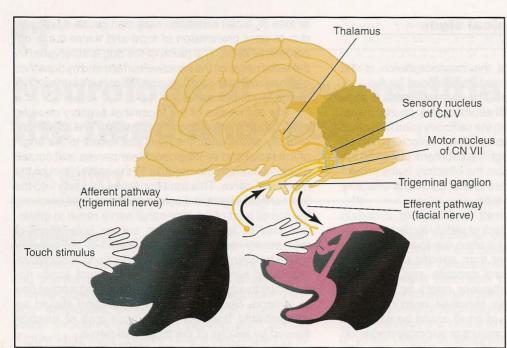
# 'Dropped jaw'

Weakness of the jaw may be manifested as a reduction in voluntary movement of the jaw causing dysphagia or a complete loss of jaw muscle tone with no ability to close the mouth (Figure 11.4). Inability to close the mouth implies a *bilateral* lesion affecting the motor component of CN V since a unilateral lesion will not cause sufficient weakness to prevent mouth closure. The bilateral nature of the trigeminal lesion implies that it involves the peripheral nerves rather than the brainstem (since a lesion in the brainstem large enough to affect both trigeminal nuclei would likely be fatal).





(a) Schematic illustration of CN V (trigeminal nerve) and its branches. (b) Areas of cutaneous innervation of the head supplied by the branches of CN V.



The palpebral 11.3 reflex is elicited by touching and stimulating the skin of the medial and lateral canthus of the palpebrae. The sensory (afferent) portion of the pathway enters the brainstem via CN V (trigeminal nerve) and synapses in the sensory nucleus within the pons. The motor (efferent) portion of the pathway (CV VII, facial nerve) is then stimulated, which causes a palpebral blink response. This is an interneuron facilitated reflex. There is also central recognition of the sensory stimulus from the trigeminal sensory nucleus.



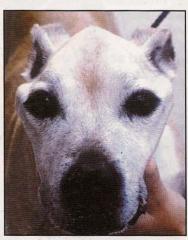
A 3-year-old male greyhound presented with an acute onset of dropped jaw due to an underlying inflammatory disease of the central nervous system.

The motor neurons of CN V are located in the pons near the rostral cerebellar peduncles and their axons are distributed to the muscles of mastication by the mandibular branch of CN V.

It is important to differentiate a lesion affecting only the trigeminal nerves from one affecting multiple cranial nerves since both may cause an animal to drool. This can be achieved by examining the animal's ability, when its mouth is held partially closed, to use its tongue and swallow food, functions mediated by CN XII (hypoglossal nerve) and CN IX (glossopharyngeal nerve), respectively, and which are not affected in uncomplicated motor trigeminal neuropathy. Apparent inability to close the mouth must also be distinguished from the unwillingness to close the mouth that can be caused by painful conditions of the head, such as masticatory muscle myositis, retrobulbar lesions, temporomandibular disease or craniomandibular osteopathy.

# Atrophy of the masticatory muscles

Masticatory muscle atrophy can occur bilaterally or unilaterally (Figure 11.5). In spite of dramatic muscle atrophy, the ability to close the mouth usually appears unimpaired. However, mouth opening may be very limited in cases where there has been muscle inflammation and subsequent fibrosis.



Severe atrophy of the masticatory muscles affects the profile of the dorsal aspect of the head. Enophthalmos may also occur and can cause periodic protrusion of the third eyelids.

Masticatory muscle atrophy can result from impaired innervation due to lesions of the motor branch of CN V, lesions of the muscles themselves or systemic disorders, such as cachexia or hyperadrenocorticism (or exogenous steroid administration). Unilateral loss of temporal muscle mass can occur in the absence of any sensory signs.

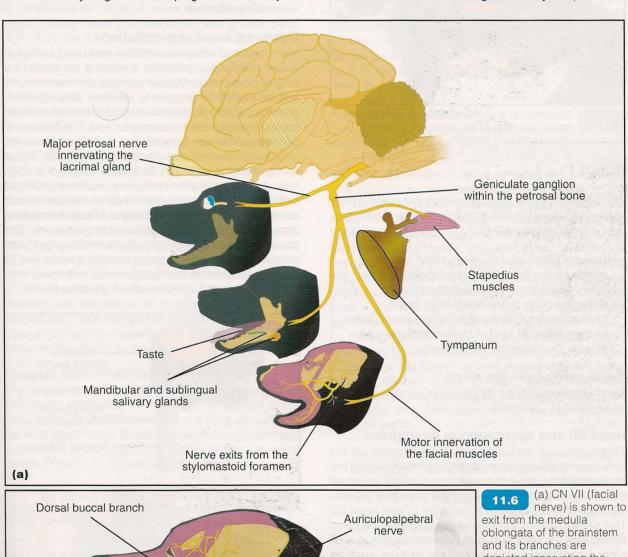
#### Abnormal facial expression

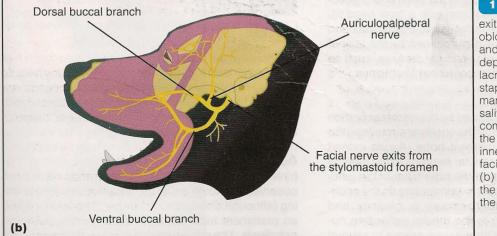
Muscles that control facial expression and maintain the normal appearance of the palpebral fissures and mouth are innervated by the facial nerve. The neurons are located in the facial nuclei of the rostral medulla and axons leave the ventrolateral surface of the medulla

ventral to CN VIII (vestibulocochlear nerve). CN VII (facial nerve) enters the petrosal bone through the internal acoustic meatus on the dorsal aspect of CN VIII and emerges from the skull through the stylomastoid foramen (Figure 11.6).

Acute damage to the facial nerve in small animals causes widening of the palpebral fissure (in contrast to the narrowing observed in affected horses) and laxity of the facial muscles of expression, often termed 'facial paresis'. The lip may droop on the affected side and food or saliva may fall from that side of the mouth (Figure 11.7). The nasal philtrum can be deviated to the normal side in the early stages and drooping of the ears may be

apparent in some breeds. Loss of the palpebral and corneal reflexes predisposes the animal to exposure keratitis. With chronicity there can be narrowing of the palpebral fissure, widening of the mouth and, in unilateral cases, deviation of the nostrils towards the affected side. The striking appearance of hemifacial spasm can be differentiated from chronic contracture by observing intact blink reflexes. In contrast to disease of CN VII itself, release of upper motor neuron (UMN) inhibition on this nerve (e.g. tetanus intoxication) causes an increase in muscle tone, producing a wide 'grimacing' mouth and narrowing of the palpebral fissures (through lateral distraction of the lateral margin of the eyelids).





exit from the medulla oblongata of the brainstem and its branches are depicted innervating the lacrimal glands, the stapedius muscle and the mandibular and sublingual salivary glands. The main component of CN VII exits the stylomastoid foramen to innervate the muscles of facial expression.

(b) Schematic illustration of the superficial branches of the facial nerve.



Weakness in muscles of facial expression will cause drooping of the lip, widening of the palpebral fissure and poor movement of the pinna. This can be observed even in loose-skinned breeds, such as the Boxer.

There are some signs for which pet owners may seek veterinary attention that do not immediately suggest a facial nerve lesion:

- Owners will sometimes report that they have observed the third eyelid flicking over the eye; in these cases the animal substitutes globe retraction (with concomitant third eyelid protrusion) for blinking with the paralysed lids
- Accumulation of food in cheeks that have poor muscle tone may lead to halitosis.

#### Keratoconjunctivitis sicca

Keratoconjunctivitis sicca ('dry eye') is discussed in more detail in Chapter 9.

#### Head tilt and spontaneous nystagmus

These signs are discussed in detail in Chapter 10. On very rare occasions, lesions affecting innervation of the segmental muscles in the neck may produce unilateral muscle spasm, thereby twisting the neck and producing signs that could be confused with a 'true' head tilt. This presentation can be differentiated from the head tilt induced by vestibular disturbances by the lack of other compatible signs of vestibular disease, such as pathological nystagmus or positional strabismus.

#### **Deafness**

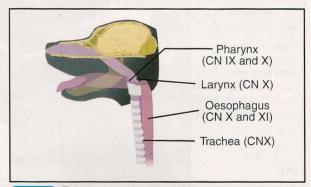
Auditory sensation is provided by the cochlear portion of CN VIII; the cell bodies of the cochlear nerve form the spiral ganglion in the petrosal bone. Axons extend proximally to join the vestibular neurons in the internal acoustic meatus and enter the brainstem at the junction of the medulla and pons, terminating on the cochlear nuclei. The central pathway is bilateral and multisynaptic projecting to the medial geniculate nucleus of the thalamus. Other axons project to several

brainstem nuclei and the caudal colliculus in the midbrain. The conscious perception of sound is served by the projection from the geniculate nucleus to the temporal lobe of the cerebral cortex, largely from the contralateral ear.

Owners usually will only recognize deafness if it affects both ears. Typically owners report that animals fail to respond to commands and sleep very heavily, only waking when they are touched. Astute owners sometimes suspect unilateral deafness; affected animals may be unable to localize the origin of noise or voice commands, even though they can be seen to react to the noise. Deafness is discussed in more detail below.

#### Dysphagia and regurgitation

Many types of lesion around the head and neck can cause dysphagia; probably the most common is a simple physical obstruction caused, for instance, by foreign bodies or neoplastic masses. Nevertheless, primary neurological dysfunction of one or multiple cranial nerves must not be overlooked. The function of CN IX and X (vagus) are integral to the function of the pharynx, larynx and oesophagus (Figure 11.8). These nerves together with CN XI (spinal accessory) originate from the same medullary nucleus (nucleus ambiguus). The rostral two-thirds of this nucleus is involved in swallowing by means of motor impulses through the glossopharyngeal and vagus nerves. The caudal nucleus ambiguus controls the laryngeal and oesophageal muscles through the vagus nerve and its branches (recurrent laryngeal nerves) with minor contributions from the spinal accessory nerve.



The pharynx, larynx and oesophagus are innervated by CN IX (glossopharyngeal nerve), CN X (vagus nerve). CN XI (spinal accessory nerve) sends a few fibres to join CN X.

Careful interrogation of the owner may help to distinguish disorders in prehension (suggesting trigeminal or hypoglossal lesions) from those in swallowing (more likely glossopharyngeal or vagus). For instance, swallowing disorders cause coughing after eating, or more commonly drinking, and there may be excessive saliva in the pharynx. On the other hand, animals that have difficulties with prehension will often have been observed spending an inordinate amount of time drinking (although often without success); this sign may be so prominent as to be interpreted by the owner as polydipsia. The gag reflex can be absent or decreased

in cases with swallowing difficulties. Inspiratory dyspnoea can be seen in conjunction with dysphagia if CN IX and X are concurrently involved.

Regurgitation must be distinguished from true vomiting; this can usually be achieved by eliciting details from the owner but also by measuring the pH of the material that is produced.

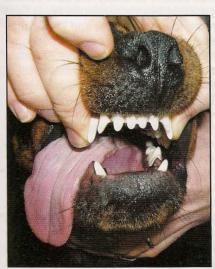
# Dysphonia and inspiratory stridor

The laryngeal muscles are innervated by branches of the vagus, and most importantly, the abductor muscles are innervated by the recurrent laryngeal nerve. Lesions affecting the recurrent laryngeal nerve frequently lead to dysphonia or signs of overt respiratory distress. Nevertheless, other conditions can also produce this sign, such as myopathies or masses in the airway. Dysphonia and laryngeal paralysis are commonly encountered as a feature of both acute and chronic generalized neuropathies (see Chapter 14).

Dysphonia may be a primary complaint of the owner but is more likely to require careful questioning to confirm. Upper respiratory tract signs may be severe enough to be noted by the owners but may be subtle in dogs presented primarily for exercise intolerance or collapse during activity. The function of the larynx is most compromised in the inspiratory phase during forced exercise. Upper respiratory tract noise associated with inspiration is called stridor and can be seen in combination with dyspnoea and cyanosis. Animals in which laryngeal function is severely compromised may require prompt interventions, ranging from provision of supplementary oxygen through to emergency tracheotomy. In addition, affected animals risk inhalation of food or water, with the consequent development of aspiration pneumonia. Concurrent deficits in function of CN IX and X greatly increase the risk of aspiration.

#### **Tongue abnormalities**

The tongue is innervated by CN XII (hypoglossal nerve). This nerve originates from cell bodies located in the medulla and exits the brainstem at a site just caudal to the accessory nerve. Bilateral weakness of the tongue is manifest by the inability to retain the tongue in the mouth (Figure 11.9). Unilateral abnormality causes



11.9

This dog has such profound tongue weakness that it cannot be withdrawn into the mouth voluntarily. Attempting to grasp the tongue may provide more information in less severe cases.

marked asymmetry of movement or muscle fasciculations in the affected side; this is best seen when a dog is panting. Animals cannot prehend food or water so may be presented for dysphagia prior to the presence of physical abnormalities. In chronic unilateral cases there may be marked atrophy and contracture of the tongue muscle causing permanent deviation towards the affected side.

#### Horner's syndrome

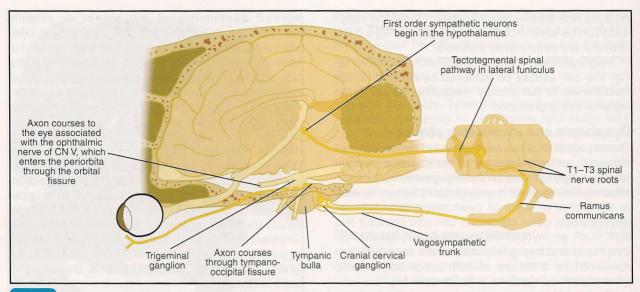
The characteristic combination of miotic pupil, prolapsed third eyelid (resulting from globe retraction; i.e. enophthalmos) and an imperfectly elevated upper eyelid comprises complete Horner's syndrome. It is not necessary for all components to be present. The most persistent sign is miosis, and the consequent anisocoria can be exaggerated by placing the animal in dim lighting conditions. This syndrome is discussed in detail in Chapter 9.

# **Autonomic anatomy**

Sympathetic nerve supply to the head, face and eye originates in nuclei in the caudal part of the hypothalamus. Axons descend through the lateral funiculus of the spinal cord to synapse with preganglionic neurons in the intermediate grey matter of the T1–T3 region of the spinal cord (Figure 11.10). The axons of these neurons ascend in the sympathetic trunk (alongside the vagus nerves) to synapse in the cranial cervical ganglion, from where they pass through the middle ear and are distributed in the ophthalmic nerve (a branch of the trigeminal) to the smooth muscle of the face. Normal tone in this smooth muscle maintains a protruded globe, wide palpebral fissure, third eyelid retraction and a degree of pupil dilation.

Parasympathetic nerve supply is contained within CN III, VII, IX and XI originating from neurons located in separate, but poorly defined, nuclei adjacent to the somatic efferent nuclei of each nerve. The parasympathetic fibres synapse in ganglia lying close to the structures they innervate. Thus, parasympathetic fibres in the:

- Oculomotor nerve synapse in the ciliary ganglion, and postganglionic fibres run along the optic nerve to innervate the ciliary muscle and constrictors of the pupil
- Facial nerve synapse in the pterygopalatine, mandibular and sublingual ganglia, and postganglionic fibres innervate the lacrimal, palatine and nasal glands and the mandibular and sublingual salivary glands (distributed via branches of the trigeminal nerve)
- Glossopharyngeal nerve synapse in the otic ganglion, and postganglionic fibres innervate the zygomatic and parotid salivary glands (distributed via branches of the trigeminal nerve)
- Vagus nerve run in the main vagal part of the vagosympathetic trunk to reach ganglia in the wall of the abdominal viscera and oesophagus.
   A few postganglionic fibres course in the internal branch of CN XI and join those of CN X.



11.10 Sympathetic innervation of the eye.

# **Lesion localization**

The cranial nerves are numbered from rostral to caudal according to the location of their nuclei (motor and/or sensory) within the brain; most of these (from trigeminal to hypoglossal) lie within the most caudal parts of the brainstem (the pons and medulla). The exceptions are: the oculomotor and trochlear nuclei, which lie within the mesencephalon (midbrain); the optic nerve, which enters the diencephalon; and the olfactory nerves, whose axons enter the telencephalon (forebrain) directly (Figure 11.11).

Therefore lesions within the brainstem, especially those within the medulla, or lesions along the course of

Lesion localization for central nervous system and peripheral nervous system causes of disorders of the face and head; the brainstem and cranial nerves are highlighted.

the peripheral nerves can all cause signs of neurological dysfunction to the head and face. It is crucial to differentiate between peripheral nerve lesions and those within the brainstem (i.e. CNS lesion) (Figure 11.12) The types of disease that affect the CNS or the PNS differ considerably in aetiology and therefore in prognosis. It should be noted here that, histologically, the optic nerve is part of the CNS and therefore is susceptible to diseases of the CNS such as granulomatous meningoencephalitis (GME).

During clinical examination the most useful test to differentiate central from peripheral lesions is evaluation of the postural reactions. Animals that have a lesion located in the brainstem are *likely*, because of the close proximity of the relevant tracts, to have deficits in postural reactions in addition to signs of cranial nerve dysfunction. Thus, for instance, a lesion located in the medulla causing facial paralysis will usually also cause deficits in postural reactions (i.e. hopping, conscious proprioception) in the ipsilateral limbs.

Unfortunately, the absence of deficits in the postural reactions cannot be used to *definitely* rule out a central lesion, since occasional lesions within the brain (and especially within the fourth ventricle) and intracranial extra-axial masses may not initially cause a concomitant postural reaction deficit. Furthermore, animals may have deficits in postural reactions because of unrelated lesions elsewhere in the nervous system.

Additional features of the neurological examination may aid in providing further evidence to differentiate brainstem from peripheral nerve disease. For instance, finding deficits in several cranial nerves located close to each other in the brainstem (e.g. CN III–VII), or perhaps finding unusual patterns of nystagmus (e.g. vertical), would suggest a CNS lesion. More general examination may suggest a specific localization, most notably the combination of Horner's syndrome, facial nerve paralysis and head tilt strongly suggests middle ear disease since that is the only site at which the three relevant neural pathways are co-located.

Neurological parameter	Peripheral cranial nerve disease	Brainstem (central) cranial nerve disease <sup>a</sup>
Consciousness	Normal	Depression; stupor; coma
Postural reactions	Normal	Frequently abnormal on ipsilateral side
Segmental spinal reflexes	May be abnormal if the underlying aetiology also causes a generalized peripheral neuropathy	Intact
Neck pain	May be a feature if the aetiology involves the nerve roots or meninges	May be a feature if the aetiology involves the nerve roots or meninges, or causes an elevation of intracranial pressure
Gait	Commonly normal unless there is a concurrent generalized peripheral neuropathy lpsilateral paresis	
Cranial nerves	Frequently just one cranial nerve involved	Multiple ipsilateral cranial nerves can be involved

Neurological examination results indicative of peripheral *versus* brainstem (central) cranial nerve disease.

<sup>a</sup> Central cranial nerve disease implies disease of the cranial nerve nuclei or the nerve roots as they leave the brainstem. Intracranial extra-axial disease affecting the cavernous sinus or retro-orbital areas can also cause signs that may be central in origin.

# **Pathophysiology**

Diseases that cause neurological abnormalities of the head and face can affect any component of the innervation, from the cell body (contained in cranial nerve ganglia or CNS) to the tips of the axons, which may lie in the CNS or PNS. Therefore there is a wide range of possible pathological insults that can be responsible for the observed deficits (and similar to those described for tetraparesis in Chapter 14). In general it is useful to subdivide the diseases into those affecting the CNS and those affecting the PNS.

## Central nervous system diseases

CNS diseases of many different types can be responsible for inducing neurological abnormalities of the head and face, particularly trauma (although brainstem signs are less common than those of the forebrain), neoplasia and the various types of encephalitis; these are reviewed in Chapters 19, 8 and 10, respectively.

#### Peripheral nervous system diseases

PNS diseases that can cause neurological abnormalities of the head and face include all those that can also cause deficits in function of the limbs (see Chapter 14). However, there are specific features of cranial innervation that render specific disease processes more likely; for instance:

- The peripheral components of the cranial nerves are generally more superficial than those elsewhere in the body and are therefore more susceptible to trauma. Nerve swelling due to any aetiology is particularly deleterious since it can cause secondary compromise of blood flow as nerves pass through foramina in the skull; the foramina themselves are susceptible to fractures
- Certain cranial nerves appear to be more susceptible to myasthenia gravis, in particular those innervating the oesophagus
- Idiopathic mononeuropathies occur more commonly amongst the cranial nerves (specifically trigeminal and facial) than other peripheral nerves.

# **Differential diagnosis**

Generally, the underlying causes of neurological abnormalities of the head and face are similar whichever nerve (or nucleus) is affected but in addition, there are a few conditions that are specific to, or more commonly affect, certain nerves. This chapter provides a description of diseases that can cause abnormalities of the head and face arranged in terms of presenting syndrome (Figure 11.13).

Syndrome	Differential diagnosis
Deafness	Congenital deafness [11] Senility (presbycusis) [11] Neoplasia of middle ear [11] Otitis media/interna [10,11] Nasopharyngeal polyp [11] Toxicity: aminoglycoside, others [11]
Laryngeal paralysis	Congenital laryngeal paralysis [11] Laryngeal paralysis polyneuropathy complex [14] Encephalitis: brainstem [10] Idiopathic laryngeal paralysis [11] Neoplasia: thyroid [11] or brainstem [8] Surgical trauma to vagus nerve [11] Toxicity (lead, organophosphate) [11]
Regurgitation/ megaoesophagus	Dysautonomia [18] Congenital megaesophagus [11] Persistent right aortic arch [11] Addison's disease [11] Polymyopathy [11, 17] Oesophagitis [11] Myasthenia gravis [17] Encephalitis: brainstem [10] Neoplasia: brainstem [8] Botulism [11, 14]

Neurological differential diagnoses for different presenting problems. The numbers in square brackets denote the chapters in the manual where these conditions are discussed in detail. CPA = cerebellomedullary pontine angle. (continues)

Syndrome	Differential diagnosis
Masticatory muscle atrophy	Idiopathic age-related atrophy [11] Neoplasia: cachexia (bilateral); CN V nerve root tumour [11]; CPA meningioma [8] (unilateral) Hyperadrenocorticism/exogenous administration of corticosteroids [11] Masticatory myositis [11] Generalized myopathies [17]
Dropped jaw	Idiopathic trigeminal nerve palsy [11] Encephalitis: brainstem [10]
Dysphagia (difficulty swallowing)	Polymyositis [17] Myasthenia gravis [17] Encephalitis: brainstem [10] Neoplasia: brainstem [8] Botulism [14]
Facial paralysis	Hypothyroidism [11] . Neoplasia: brainstem [8], middle ear [11] Idiopathic facial paralysis [11] Encephalitis: brainstem [10] Otitis media/interna [10, 11] Trauma: surgical or external [11]
Multiple cranial nerve deficits	Ipsilateral CN VII, VIII, Horner's: middle ear; otitis media/interna, neoplasia of middle ear [11] Ipsilateral CN III, IV, V, VI: cavernous sinus syndrome; neoplasia and infection [9] Multiple ipsilateral CN deficits: neoplasia; (brainstem, nerve root tumour, round cell tumour) [8]; encephalitis [10] Multiple CN deficits: neoplasia (brainstem, nerve root tumour, round cell tumour) [8]; encephalitis [10] Multiple CN deficits + generalized LMN signs: polyneuropathy [14]

(continued) Neurological differential diagnoses for different presenting problems. The numbers in square brackets denote the chapters in the manual where these conditions are discussed in detail.

CPA = cerebello-medullary pontine angle.

# **Neurodiagnostic investigation**

A complete neurological examination is a prerequisite for investigating suspected neurological disease of the head and face (and is covered in full in Chapters 1 and 2). However, several features may require particular attention and are described below (Figure 11.14).

#### History

A thorough history is essential because certain neurological disorders of the head and face may produce signs that cannot be observed by the veterinary surgeon during a consultation. For instance, if an animal is reported to be vomiting it is crucial to determine whether it is 'true' vomiting or regurgitation. The owner of any animal in which generalized weakness or exercise intolerance is reported should be questioned about the animal's vocalization since dysphonia resulting from laryngeal dysfunction occurs commonly in association with peripheral neuropathies.

#### Observations

Before conducting a 'hands on' examination, several observations may aid in recognizing or classifying disorders of the head and face. Firstly, as the animal walks around a room the position of the head and neck can be observed, looking in particular for a head tilt or generalized tremors (as these may also affect the head). Examination for symmetry provides important clues with regard to the function of the nerves innervating the musculature of the head and face; this examination focuses on the relative sizes of the masticatory muscle mass, facial expression, palpebral fissures and pupils. The ability of the animal to close their jaw (dependent on the motor component of the trigeminal nerves) and maintain a normal tongue position (mediated by the hypoglossal nerves) is also apparent from simple observation.

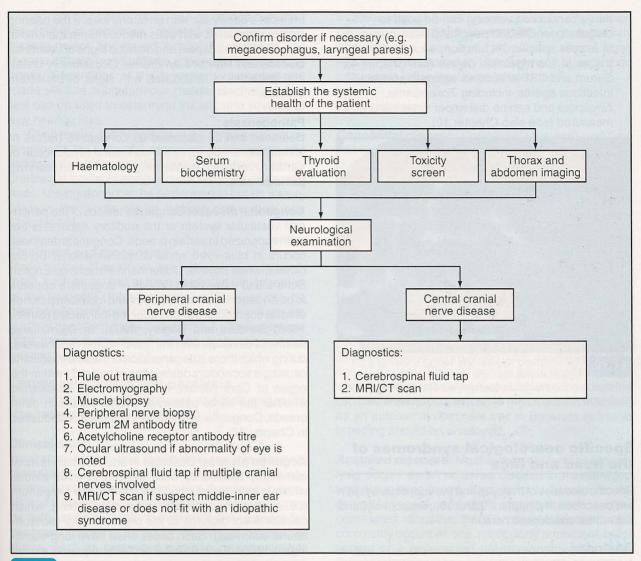
# **Neurological examination**

Important functions for assessment of innervation of the head and face include the menace response, blink (or palpebral) reflex, oculovestibular reflexes and gag reflex, all of which are described in Chapters 1 and 9. Several other tests may be of value in detecting neurological abnormalities of the head and face:

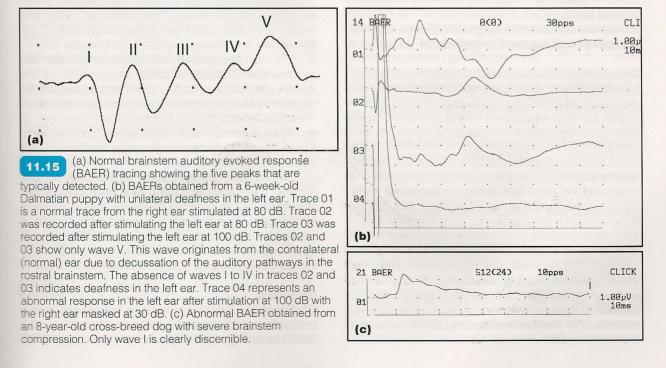
- Olfaction can be tested in a crude way by observing the response to concealed food (e.g. by blindfolding the animal)
- Masticatory muscle tone is evaluated by opening the laws
- Tongue strength is evaluated by attempting to hold the tongue; normal animals can easily withdraw the tongue (since it is wet and slippery).

# Ancillary diagnostic tests

- Hearing can be tested crudely by observing how an animal responds to noise; however, a more sophisticated and objective test is the brainstem auditory evoked response (BAER) (Fig 11.15) (see Chapter 4).
- Schirmer tear test can be used to detect deficits in tear production (see Chapter 9).
- Pharmacological testing with adrenergic agonists can be used to investigate Horner's syndrome (see Chapter 9).
- Measurement of antibodies to the acetylcholine receptor can be used to substantiate the diagnosis of immune-mediated myasthenia gravis. Currently the test in dogs and cats can only be reliably performed by a laboratory in the USA (see Chapter 17).
- Measurement of antibodies to type 2M muscle fibres can be used as an aid to diagnosis of masticatory muscle myositis.
- MRI or CT scanning can be used to detect CNS lesions, especially tumours (Figure 11.16).
- Cisternal cerebrospinal fluid (CSF) analysis can be used to detect inflammatory disease of the CNS or nerve roots (see Chapter 3).
- Electrodiagnostics (electromyography (EMG),



11.14 Diagnostic approach to cases with abnormalities of the head and face.



nerve conduction velocity) can be used to diagnose generalized peripheral neuropathies or to assess specific CN function, such as that of the facial and trigeminal nerves (see Chapter 4).

 Serum and CSF antibodies against various infectious agents, including *Toxoplasma*, *Neospora* and canine distemper virus, can be measured (see also Chapter 10).



T2-weighted sagittal MR image showing a hyperintense lesion in the brainstem of a dog that had reduced facial sensation (\*\*). The lesion was later confirmed to be granulomatous meningoencephalitis.

# Specific neurological syndromes of the head and face

Specific diseases of the eyes and the vestibular system are described in Chapters 9 and 10, respectively, and will not be considered here.

#### **Deafness**

A full list of differential diagnoses and their diagnostic features can be found in Figure 11.17.

#### Clinical signs

Owners usually detect hearing loss only if it is bilateral, although perceptive owners may notice a change in

Causes of deafness	Distinguishing diagnostic features
Congenital deafness	Usually deaf from birth; no waveforms on BAER
Neoplasia of middle or inner ear	Lysis on bulla radiographs; bulla mass on CT/MRI; cytology on myringotomy
Otitis media/interna	Abnormal otic exam; soft tissue in bulla on CT/MRI; cytology on myringotomy
Nasopharyngeal polyp	Young cats; mass visible on otic/pharyngea exam
Toxicity: (aminoglycosides, furosemide, cisplatin)	History of exposure; rule out other causes

Specific diagnostic features of different causes of deafness. BAER = brainstem auditory evoked response; CT = computed tomography; MRI = magnetic resonance imaging.

their pet's behaviour with unilateral loss. If the hearing loss is associated with otitis media/interna the animal may show signs of pain and develop signs of vestibular disease and Horner's syndrome. Occasionally unilateral deafness is associated with signs of brainstem disease.

#### **Pathogenesis**

Deafness can be classified as conductive (failure of conduction of sound) or sensorineural (dysfunction of sensory organ) depending on the underlying pathogenesis.

Congenital disease: Congenital lesions of the peripheral vestibular system or the auditory apparatus are well recognized in certain breeds. Congenital deafness occurs in blue-eyed white cats, Dalmations, Border Collies, white Boxers, Dobermann Pinschers, English Setters and many other breeds of dog; there appears to be an association of blue eyes and localized patches of white coat colour in many affected individuals (Strain, 1996; Sanders and Bagley, 2003). In Dalmatians, deafness develops over the first 3-4 post-natal weeks, during which there is degeneration of the stria vascularis causing a secondary destruction of hair cells within the organ of Corti (Strain, 1996); it is not established whether the same pattern of events occurs in other breeds. Congenital vestibular dysfunction is discussed in Chapter 10.

Acquired disease: Deafness in adult animals is most commonly caused by otitis externa or otitis media, which impairs conduction of sound to the tympanum (i.e. conductive deafness) or by otitis interna, which causes direct damage to the organ of Corti (sensorineural deafness). Such cases often have long-standing evidence of ear disease and will frequently exhibit pain or irritation in the region of the ears; however, otitis cannot be ruled out simply because of an absence of otoscopically detectable disease. Older animals occasionally develop tumours in the middle ear cavity, and nasopharyngeal polyps (an inflammatory lesion) are sometimes found in young cats (see Chapter 10).

It is well recognized that geriatric animals can become deaf because of senile degeneration of the middle ear ossicles (Strain, 1996) or age-associated degeneration of the organ of Corti, termed presbycusis (Knowles *et al.*, 1989). Sensorineural deafness in young adults is most likely to be caused by exposure to toxins, in particular aminoglycoside antibiotics and cisplatin.

Diseases affecting the ascending pathways through the brainstem, such as trauma, neoplasia or encephalitis, rarely cause complete deafness, and other signs of brainstem disease tend to overshadow any loss of hearing that does occur. On rare occasions, middle ear infections can extend through the temporal bone to invade the intracranial cavity.

#### Diagnosis

Confirmation of deafness caused by disease in the brainstem, middle or inner ear is readily achieved by BAER recordings (see Figure 11.15) (see Chapter 4).

During this procedure, which can be carried out when the animal is conscious, sedated or anaesthetized, clicking noises are played through headphones into the ear canals (or vibrations applied to the temporal bone). Recordings of the brainstem responses are made via fine subcutaneous needle electrodes. The test can be used to determine the site and severity of any hearing loss.

Otitis media and neoplasia of the middle ear can be diagnosed by a careful otoscopic examination and radiography, although MRI and CT scanning are increasingly available and are more sensitive diagnostic tests. Myringotomy can be performed to obtain a sample from the middle ear for cytology and culture (see Chapter 10).

#### Treatment and prognosis

Many causes of deafness are not amenable to treatment, such as genetic or toxin-mediated degeneration of the hair cells. Infection in the middle ear can be treated with antibiosis or, more commonly, will require surgical treatment (bulla osteotomy). Following severe otitis media there may never be restoration of full hearing acuity.

# Laryngeal paresis and paralysis

A full list of differential diagnoses and their diagnostic features can be found in Figure 11.18.

#### Clinical signs

Inspiratory stridor and dysphonia are the classical clinical signs associated with laryngeal paresis or paralysis, although severe inspiratory dysphoea, cyanosis and collapse occur occasionally. These signs may be sufficiently mild that animals will only present for treatment following particular periods of respiratory stress, such as prolonged exercise or extreme hot

Causes of laryngeal paresis and paralysis	Distinguishing diagnostic features	
Congenital laryngeal paralysis	Specific breed; early onset; rule out other causes	
Laryngeal paralysis polyneuropathy complex	Specific breed; progressive LMN tetraparesis; rule out other causes	
Neoplasia: thyroid	Presence of thyroid mass	
Idiopathic laryngeal paralysis	Rule out other causes	
Surgical trauma to vagus nerve	Recent history of neck surgery	
Toxicity (lead, organophosphate)	History of exposure; blood lead levels; blood cholinesterase activity	
Brainstem disease (neoplasia, encephalitis)	Presense of other signs of brainstem disease; CT/MRI of brain; CSF analysis	

Specific diagnostic features of different causes of laryngeal paresis and paralysis.

CSF = cerebrospinal fluid; CT = computed tomography;

LMN = lower motor neuron; MRI = magnetic resonance maging.

weather, at which time they may present in a hyperthermic crisis. Affected animals may also cough, especially when drinking water, and can develop clinical signs related to the secondary development of aspiration pneumonia (after they have inhaled food).

#### **Pathogenesis**

Congenital disease: Congenital laryngeal paralysis has been proven or suspected in several breeds including Bouviers des Flandres, Siberian Huskies, Husky crosses, Dalmatians and Bull Terriers (see Appendix 1). Congenital laryngeal paralysis may be accompanied by a generalized peripheral neuropathy in which case it is termed laryngeal paralysis polyneuropathy complex (LPPC) (see Chapter 14) (Braund et al., 1994). In Bouviers and Huskies there is evidence of degeneration of neuronal cell bodies within the nucleus ambiguus in the medulla oblongata (Venker-van Haagen et al., 1978; O'Brien and Hendriks, 1986) with subsequent Wallerian-like degeneration of the laryngeal nerves; whereas in Dalmatians (Braund et al., 1989) and Rottweilers (Mahony et al., 1998) it occurs as part of a generalized 'dying back' axonal degeneration. The onset of clinical signs in these dogs can be as early as 4-6 months of age, at which time the condition can be unilateral or bilateral. As the disease is inherited as an autosomal dominant trait in Bouviers selective breeding should be employed.

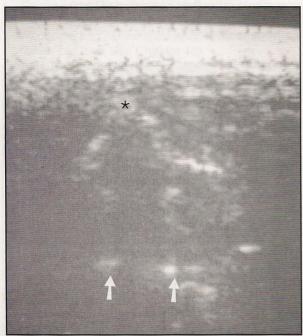
Acquired diseases: Most commonly laryngeal paralysis occurs as an acquired disease in middle-aged and older large-breed dogs, notably Labradors. Although laryngeal paralysis in mature animals is often considered idiopathic there is some evidence that it commonly occurs as one, particularly prominent, component of a generalized polyneuropathy. Since the recurrent laryngeal nerve is especially long it has been proposed that it is more susceptible than other peripheral nerves to axonal 'dying back' diseases, in which transport of vital substances to the tip of the axon is compromised. Therefore it is important to consider an investigation for systemic diseases that can cause polyneuropathies (see Chapter 14).

Acquired laryngeal paralysis occasionally occurs as a consequence of trauma to the vagus nerve during cervical surgery, lead and organophosphate toxicity, retropharyngeal infection and neoplasia in the vicinity of the recurrent laryngeal nerve; the most commonly incriminated tumour type is thyroid carcinoma. Laryngeal paresis and/or paralysis can occasionally result from brainstem disease; in these cases other cranial nerves are usually involved and there is often a profound alteration of the dog's consciousness.

#### Diagnosis

Laryngeal paralysis is usually diagnosed simply by examination of the movement of the vocal folds, either directly through the mouth when the animal is lightly anaesthetized or by ultrasound examination when conscious (Figure 11.19). In equivocal cases EMG examination is helpful, not only in objectively defining denervation of the larynx but also in detecting more

generalized disease both of cranial structures (especially the pharynx) and throughout the entire body. Palpation, ultrasonography and biopsy can readily diagnose thyroid tumours.



Poor abduction of the arytenoid cartilages during inspiration can often be detected by real-time ultrasound examination. Note the position of the cuneiform processes (arrowed). \* indicates thyroid cartilage.

#### Treatment and prognosis

Treatment of laryngeal paralysis requires surgical lateralization of the arytenoid cartilage (Monnet, 2003) regardless of the underlying cause as it is usually a permanent defect. Nevertheless, surgical lateralization of the arytenoids should not be undertaken lightly in cases where deglutition is compromised since it will dramatically increase the risk of food inhalation. Surgery is only a short-term measure in those breeds with concurrent progressive tetraparesis. Some thyroid tumours can be excised surgically but others are extremely locally invasive, implying that other anti-cancer treatment modalities should be considered.

#### Megaoesophagus

A full list of differential diagnoses and their diagnostic features can be found in Figure 11.20.

#### Clinical signs

The characteristic sign of megaoesophagus is regurgitation, usually involving both food and fluid. During the initial investigation it is critical to differentiate regurgitation from true vomiting. Due to regurgitation there may be several other associated clinical signs such as weight loss (or failure to gain weight) and coughing because of aspiration pneumonia.

#### **Pathogenesis**

There are both congenital and acquired forms of megaoesophagus.

Causes of megaoesophagus	Distinguishing diagnostic features	
Dysautonomia	Other signs of autonomic dysfunction	
Congenital megaoesophagus	No other neurological deficits; certain breeds predisposed	
Persistent right aortic arch	Radiographic appearance	
Addison's disease	Generalized weakness; electrolyte abnormalities; negative ACTH stimulation test	
Myasthenia gravis	± Exercise intolerance; response to tensilon test; positive ACh receptor antibody titre	
Polymyositis	Generalized weakness; increased CK; generalized EMG abnormalities; myositis or muscle biopsy	
Oesophagitis	History of vomiting; endoscopic evidence	
Botulism	Generalized LMN signs	
Brainstem disease (neoplasia, encephalitis)	Other signs of brainstem disease; CT/MRI of brain; CSF analysis	

Specific diagnostic features of different causes of megaoesophagus. ACh = acetylcholine; ACTH = adrenocorticotropic hormone; CK = creatine kinase; CSF = cerebrospinal fluid; EMG = electromyography; LMN = lower motor neuron.

Congenital disease: The underlying cause of congenital megaoesophagus is unknown but recent studies have suggested that afferent function may be aberrant (Holland et al., 1996, 2002). Congenital megaoesophagus can also arise as a secondary consequence of a persistent right aortic arch or as one aspect of congenital myasthenia gravis (although not all affected breeds develop megaoesophagus).

**Acquired disease:** Acquired megaoesophagus can result from a wide range of lesions including both brainstem and systemic disease, most notably myasthenia gravis, in which there is immune-mediated destruction of the acetylcholine receptor.

#### Diagnosis

Megaoesophagus is readily diagnosed by radiography, especially if food mixed with barium is given shortly before scanning (Figure 11.21). Determining the cause of megaoesophagus relies on detecting and investigating other signs of systemic or brainstem disease. For instance, routine blood analysis and blood chemistry can suggest hypoadrenocorticism, myositis or systemic lupus erythematosus. Hypothyroidism and myasthenia gravis can be detected by specialist blood tests. If the neurological examination detects generalized peripheral nerve diseases, then botulism or generalized peripheral neuropathies (see Chapter 14) may be considered; if nearby cranial nerves show deficits, then brainstem disease may be suspected and diagnosed using advanced imaging techniques or CSF analysis.

The possibility of dysautonomia should be considered, particularly if other signs of autonomic dysfunction are evident. If all of these conditions can be ruled out then idiopathic disease must be assumed.



Megaoesophagus confirmed by administration of barium mixed with food.

# Treatment and prognosis

For many acquired cases of megaoesophagus, treatment of the underlying disease is possible, for example by immunosuppressive therapy using corticosteroids or other drugs for SLE and polymyositis. With congenital myasthenia gravis, although the disease can be treated using anticholinesterases, it can be difficult to achieve the correct dose to restore satisfactory swallowing function (Miller *et al.*, 1983). Similarly, unless persistent aortic arches are surgically treated early the megaoesophagus will not resolve adequately.

No matter what the cause, postural feeding (i.e. feeding the animal with their head directly above their stomach) and feeding a diet that is of a gelatine-like consistency is highly recommended to aid passage of food from mouth to stomach and avoid inhalation.

The prognosis for animals affected with megaoesophagus is guarded because of the very high incidence of aspiration pneumonia, which is life-threatening. Many animals succumb within a few weeks to months of starting therapy. It has been suggested that since spontaneous remission can occur in myasthenia gravis it may be preferable to avoid immunosuppressive therapy because it may promote respiratory tract infection (Shelton, 2002) (see Chapter 17).

# Changes in muscles of mastication

A full list of differential diagnoses and their diagnostic features can be found in Figure 11.22.

#### Clinical signs

Atrophy of the masticatory muscles can occur unilaterally or bilaterally. Bilateral atrophy is not associated with failure to close the mouth but some individuals will exhibit limited mouth opening (trismus). Third eyelid protrusion may follow severe temporal and masseter muscle atrophy resulting in enophthalmos (due to loss of muscle support to the orbit) and may impair vision. Swelling of the muscles of mastication can occur in the

Causes of changes in muscle of mastication	Distinguishing diagnostic features	
Age-related atrophy	Rule out other causes	
Hyperadrenocorticism or exogenous administration of corticosteroids	Other signs of hyperadrenocorticism: elevated alkaline phosphatase; positive ACTH stimulation test; recent history of corticosteroid administration	
Neoplasia: cachexia (bilateral); CN V NRT or CPA meningioma (unilateral)	Development of ipsilateral facial sensory deficits and neurogenic keratitis; spontaneous activity on EMG; presence of mass on imaging of the brain (CT/MRI)	
Masticatory myositis	May have muscle pain and swelling at onset of signs; antibodies against type 2M myofibres; inflammatory infiltrate on muscle biopsy; elevated CK; difficulty opening jaw	
Generalized myopathies	Signs of a generalized myopathy (see Chapter 17)	

Specific diagnostic features of different causes of changes in the muscles of mastication.

ACTH = adrenocorticotropic hormone; CK = creatine kinase; CPA = cerebello-medullary pontine angle; CS = corticosteroids; CT = computed tomography; EMG = electromyography; MRI = magnetic resonance imaging; NRT = nerve root tumour.

acute phase of masticatory myositis with trismus and exophthalmos. Palpation of the muscles or attempts to open the jaws can cause a painful response. Exophthalmos in the absence of swelling of the muscles of mastication can result from myositis of the extraocular muscles. Young Golden Retrievers appear to be predisposed to this unusual disease (see Chapter 9).

#### **Pathogenesis**

Differential diagnoses for masticatory muscle atrophy include all the causes of generalized myopathies (see Chapter 17) as well as diseases of the trigeminal nerve (CN V) or its nucleus. The absence of other detectable neurological deficits confirms that brainstem involvement is improbable in most cases.

**Bilateral atrophy:** Bilateral atrophy can be caused by many systemic diseases, most notably cachexia (e.g. in association with cancer) and prolonged influence of exogenous or endogenous corticosteroids (e.g. hyperadrenocorticism).

However, most commonly it occurs as a consequence of masticatory myositis because of destruction of muscle fibres and scarring, which can occur rapidly. This is an immune-mediated disorder in which antibody-directed inflammation is targeted at the muscles of mastication, which include the masseters, temporalis and pterygoid muscles. The specific antigen is part of the unique myofibre type (type IIM) contained within these muscles. There is no gender predisposition documented for masticatory myositis and the only breed noted to have a predisposition is the German Shepherd Dog. Most affected dogs are of large breeds and are often young adults; cats are infrequently affected by this condition.

**Unilateral atrophy:** Unilateral atrophy is occasionally encountered and although many animals live for many years without developing other signs it is now recognized that nerve sheath tumours can be responsible (Bagley *et al.*, 1998).

#### Diagnosis

Detection of significant levels of anti-type IIM muscle fibre antibodies will confirm masticatory myositis, although by the time animals reach the chronic phase the antibody response may well have subsided. Serum creatine kinase levels may also be elevated. Muscle biopsy may reveal an inflammatory infiltrate, myofibre necrosis and phagocytosis and specifically identify antibody localization to the type IIM myofibres. Electromyography will often identify spontaneous abnormalities and should always be performed to evaluate the rest of the patient's musculature in cases where a more generalized myopathy is suspected. MR or CT imaging of the brain should be performed in all cases with unilateral masticatory muscle atrophy.

#### Treatment and prognosis

Usually, masticatory muscle atrophy as a result of systemic diseases, such as hyperadrenocorticism, does not appear to be reversible but does not often cause significant deficits.

Masticatory myositis is treated by immunosuppressive doses of corticosteroids but some cases of masticatory muscle atrophy are too far advanced for this therapy to be effective. The recommended dose of prednisolone is 1–2 mg/kg orally q12h for 3–4 weeks, after which the dosage is tapered slowly to achieve the lowest dosage q48h that will eliminate the clinical signs. Most dogs treated aggressively in the early stages show a good response to this therapy but relapses are possible. Some cases will require the addition of a further immunosuppressive medication, such as azathioprine (see Chapter 17).

While cases that respond rapidly often have a favourable prognosis, chronic loss of muscle may lead to trismus and permanent dysphagia. Feeding regimens should be discussed with the owner as even in the early stages of a responsive condition feeding tubes may be necessary, if only to reduce the potential for aspiration pneumonia. Additional therapy advisable includes vigorous physiotherapy of the jaw muscles; this can be done by encouraging the dog to chew rawhide or play with tennis balls.

#### Idiopathic trigeminal nerve palsy

#### Clinical signs

Motor deficits caused by trigeminal nerve palsy are recognized in the syndrome of 'dropped jaw', in which the patient (almost always a dog) cannot close the mouth or prehend food properly. Other cranial nerves are not affected but there can be a variable degree of sensory loss (sensory trigeminal distribution) and some animals display Horner's syndrome (Mayhew *et al.*, 2002).

#### **Pathogenesis**

The cause is thought to be an idiopathic neuritis, although older texts suggested an unsubstantiated link with dogs carrying heavy loads in their mouths.

#### Treatment and prognosis

Treatment is simply supportive, helping the animal to eat by offering boluses of soft food and assisting with drinking or the placement of a temporary feeding tube. It has been suggested that holding the mouth partially closed with a muzzle facilitates eating and drinking during recovery. Most animals recover rapidly and are able to eat unassisted within 3 weeks.

#### Facial paralysis

Facial nerve dysfunction may be due to disease of the peripheral facial nerve (CN VII) caused by otitis media/interna (see Chapter 10), trauma, hypothyroidism, neoplasia of the middle/inner ear or polyneuropathies (see Chapter 14). Disease of the facial nerve nucleus in the medulla of the brainstem can result from any of the diseases affecting the CNS. The most common cause of peripheral facial nerve paralysis has been reported to be idiopathic (75% of dogs and 25% of cats with facial paralysis). A full list of differential diagnoses and their diagnostic features can be found in Figure 11.23.

#### Idiopathic facial paralysis

Clinical signs: Idiopathic facial nerve paralysis or palsy may be unilateral or bilateral, but usually occurs in the absence of other neurological deficits (some-

Causes of facial paresis	Distinguishing diagnostic features	
Myasthenia gravis	Regurgitation, megaoesophagus, exercise intolerance; response to tensilon test; positive ACh receptor antibody titre	
Hypothyroidism	Other signs of hypothyroidism, decreased T4 and elevated TSH levels	
Neoplasia of middle or inner ear	Lysis on bulla radiographs, bulla mass on CT/MRI, cytology on myringotomy	
Idiopathic facial paralysis	Normal tear production; rule out other causes	
Otitis media/interna	May have decreased tear production, abnormal otic exam, soft tissue in bulla on CT/MRI, cytology on myringotomy	
Trauma: surgical or external	Recent history of trauma or surgery	
Brainstem disease (neoplasia, encephalitis)	Other signs of brainstem disease, CT/MRI of brain, CSF analysis	
Other generalized LMN diseases	Generalized signs of LMN dysfunction	

Specific diagnostic features of different causes of facial paresis. ACh = acetylcholine; CSF = cerebrospinal fluid; CT = computed tomography; LMN = lower motor neuron; MRI = magnetic resonance imaging; T4 = thyroxine; TSH = thyrotropin (thyroid-stimulating hormone).

times affected animals also develop idiopathic vestibular syndrome). Exposure keratitis can occur subsequent to the improper lubrication of the cornea despite normal tear production. Clinical signs are usually maximal in 7 days and recovery can take 3–6 weeks if it occurs at all. Since unilateral facial nerve palsy can also develop in association with CNS diseases it is essential to consider the possibility of CNS lesions; typically these will be associated with abnormalities of the postural reactions (see Lesion localization).

**Pathogenesis:** In early reports on idiopathic facial nerve palsy, biopsy revealed marked depletion of large diameter myelinated axons (Braund *et al.*, 1979).

**Diagnosis:** All possible causes of facial paresis and/or paralysis should be excluded before this specific diagnosis can be made. A thorough investigation for ear disease should take place in addition to blood tests for hypothyroidism and electromyography to rule out polyneuropathies.

Treatment and prognosis: There is no effective treatment for the underlying disease but it is important to ensure that the cornea is adequately lubricated (either by endogenous production or eye drops). The prognosis for idiopathic facial palsy varies, many animals make a gradual recovery (weeks to months) but some will be left with permanent deficits. These deficits may progress to produce muscle contracture and deform the facial expression permanently. This can be mistakenly interpreted as hemifacial spasm, an uncommon syndrome in dogs and cats.

# Hemifacial spasm

Clinical signs of this syndrome include blepharospasm, elevation of the ear, deviation of the nose to the affected side and wrinkling or displacement of the upper lip. The signs may precede facial paralysis but the spasm must be differentiated from contraction secondary to denervation atrophy and fibrosis. Hemifacial spasm may be due to lesions of the middle/inner ear or the brainstem and should be investigated thoroughly. Control of hemifacial spasm depends on identifying and treating the underlying cause.

# Multiple cranial nerve problems

Various combinations of unilateral or bilateral cranial nerve deficits are sometimes detected; almost any combination of signs is possible depending on the underlying cause (see below). In some instances there will be concomitant depression in limb postural reactions and some animals may exhibit stupor.

It is important to recognize the significance of bilateral cranial nerve disorders and postural reaction deficits: bilateral cranial nerve deficits suggest that the lesion is not in the CNS (a lesion in the brainstem large enough to cause bilateral deficits would probably be fatal), and postural reaction deficits in combination with cranial nerve deficits suggest that the lesion is in the CNS.

Generalized peripheral neuropathies (see Chapter 14) can cause any combination of cranial nerve

deficits, therefore, it is of the utmost importance to examine all peripheral nerve reflexes in any animal that has a cranial nerve disorder. Occasionally the most prominent signs are confined to the cranial nerves, for instance there are uncommon idiopathic diseases that can affect multiple cranial nerves, most notably:

- Feline dysautonomia, in which pupillary dilation and megaoesophagus are characteristic signs (see Chapter 18)
- Polyganglioneuritis, which has been reported as a cause of multiple somatic cranial nerve deficits (see Chapter 14).

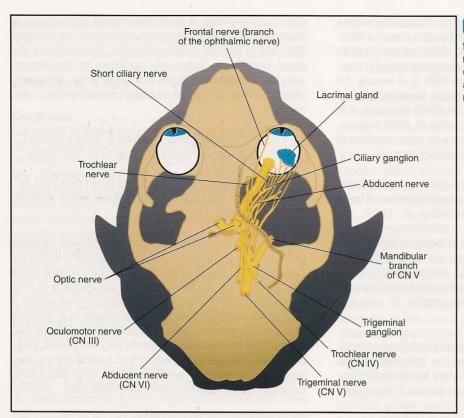
Brain tumours may occasionally cause multiple cranial nerve signs, especially if they develop within the caudal part of the brainstem; in most instances these signs would be accompanied by depression in limb postural reactions. A more confusing presentation is that associated with skull-base tumours (e.g. cavernous sinus syndrome, see Chapter 9) where there may be multiple cranial nerve deficits (Figure 11.24), often bilaterally, but without evidence of brainstem involvement. Such animals are often also very depressed because of elevated intracranial pressure.

#### Miscellaneous disorders

#### latrogenic cranial nerve lesions

Several cranial nerves and associated structures are susceptible to injury during surgical procedures around the head and neck.

- The facial nerve is vulnerable because of its superficial location on the side of the face.
   Surgery around the deep portions of the external auditory canal and the middle ear, or parotid duct transposition are common causes of facial nerve palsy. Clinical signs due to neurapraxia usually improve within 2 weeks.
- The sympathetic trunk is vulnerable to injury during bulla osteotomy (especially in cats) and during any deep neck surgery that involves prolonged retraction of the soft tissues, including the sympathetic trunk where it is contained within a common sheath alongside the vagus nerve.
   Occasionally dogs appear to develop Horner's syndrome after vigorous restraint using choke chains.
- The recurrent laryngeal nerve may be injured during approaches to, or around, the trachea (especially extraluminal stenting procedures for tracheal collapse).
- The hypoglossal nerve is susceptible to injury during mandibular surgery, especially hemimandibulectomy. Bilateral injury can lead to dramatic drooping of the tongue from the mouth.
- The peripheral vestibular system can be damaged by over-vigorous curettage during bulla osteotomy.



A schematic illustration of the nerve supply to the eye and its surrounding muscles and structures, demonstrating the close approximation of multiple cranial nerves at the base of the skull.

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# Tremor and involuntary movements

Rodney S. Bagley

# Introduction

Involuntary movement disorders result in some of the most dramatic clinical presentations in veterinary medicine. Classically, these disorders are present during periods of inactivity rather than during voluntary movement. Cerebellar disease, conversely, can result in apparent involuntary abnormalities during movement. Some involuntary movements are persistent while others are episodic. Certain involuntary movements have characteristics that allow for identification of specific causes, whereas others are only a reflection of dysfunction of the nervous or musculoskeletal systems. Clinically, it is important to first identify the type of involuntary movement present. Subsequently, a more directed approach can be used to establish the cause of the movement disorder.

# **Clinical signs**

Involuntary movement disorders are less well classified in animals than in humans. Terms such as tics, twitches, shivering, shuddering and fasciculation are often used to describe episodic, irregular muscle contractions. They are usually manifested through abnormal motion of the limbs, trunk or head. There are seven forms of involuntary movement.

#### Myoclonus

Myoclonus is a shock-like contraction of a muscle or muscles that tends to occur repeatedly in a rhythmic pattern (Breazile et al., 1966) and may persist during sleep. It is akin to the rhythmic depolarization and contraction that occurs in the heart with each beat. Myoclonus can be focal, multifocal or generalized. It often presents in the thoracic limbs, however, the pelvic limbs or the facial muscles (including the tongue) may also be involved. Myoclonus may be physiological (such as that seen when falling asleep or during sleep), epileptic or symptomatic associated with central nervous system (CNS) disease. An idiopathic, essential myoclonus has been recognized in people but has not been described in veterinary medicine. Myoclonus in dogs is usually the result of distemper infection, which establishes a pacemaker-like depolarization of local motor neurons; however, it has been associated with lead toxicity and other causes of CNS inflammation Breazile et al., 1966).

#### Seizures

Seizure activity also results in spontaneous involuntary movements. With generalized seizures, the clinical pattern is fairly characteristic including falling to a lateral recumbent position, rigidity and eventually paddling or gaiting movements of the limbs. With focal seizures, however, localized involuntary movements such as twitching of a single limb or part of the face may be present. Electroencephalography (EEG) must be performed at the time of the movement to confirm the cerebral aetiology of the disorder, but this is rarely practical in veterinary medicine. A detailed discussion of seizures can be found in Chapter 7.

#### **Tremor**

Tremor is one of the most common involuntary movement disorders in humans and is also surprisingly common as a clinical abnormality in dogs. Tremor is an involuntary, rhythmic, oscillating movement of fixed frequency resulting from alternate or synchronous contraction of reciprocally innervated antagonistic muscles (Jankovic and Fahnn, 1980). It can be focal, affecting just one limb or the head for example, or generalized. Electromyographically, tremor is characterized by rhythmic bursts of motor neuron activity occurring in opposing muscle groups. The contraction of muscles with opposing function gives tremor a biphasic nature. This biphasic character differentiates tremor from other abnormalities of movement. While seen during the awake state, true tremor should cease with sleep. As for myoclonus, tremors may be physiological, idiopathic (or essential) such as that seen in senile tremor of dogs, or pathological due to a nervous system disease.

#### Intention tremor

An intention tremor occurs or is worsened when the animal intends to perform a function in a goal-oriented manner. This type of tremor is usually most evident when the animal attempts to eat or drink. An intention tremor usually occurs at a frequency of between 2 and 6 times a second, and is most often associated with disease of the cerebellum. Other signs of cerebellar disease that accompany cerebellar tremor include ataxia (incoordination, swaying from side to side); dysmetria ('goose-stepping', overflexing of the limbs when walking); menace deficits (with normal vision and pupillary light reflexes); head tilt; nystagmus (Holliday 1979/1980; de Lahunta, 1983); truncal sway; and infrequently anisocoria (see Chapter 2).

#### Dyskinesia

Dyskinesia is defined as impairment of the power of voluntary movements resulting in fragmented or incomplete movements (Ramsey *et al.*, 1999; Penderis and Franklin, 2001). Dogs reported with these abnormalities may adopt abnormal postures, such as holding up a limb in an attempt to move or adopting a kyphotic posture of the spine without being able to initiate movement. The pathophysiological mechanisms underlying these movements are poorly understood, but may represent a central neurotransmitter or pathway abnormality or possibly a local muscular abnormality.

#### Myokymia and neuromyotonia

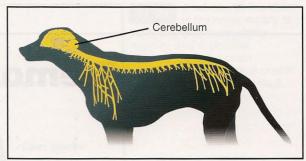
Myokymia and neuromyotonia refer to the involuntary rippling of muscles that persists even during sleep and under anaesthesia. These disorders represent a continuum of signs that result from motor axon or terminal hyperexcitability. This hyperexcitability can be caused by a wide variety of disorders of the CNS and peripheral nervous system (PNS) but is particularly related to changes in ion channel function. Electromyography (EMG) studies of myokymia reveal short bursts of ectopically generated motor unit potentials, firing at rates of 5-62 Hz and appearing as doublets, triplets or multiplets. These bursts fire rhythmically or semirhythmically and sound like soldiers marching. Neuromyotonia is characterized by muscle stiffness and persistent contraction related to underlying spontaneous repetitive firing of motor unit potentials. On EMG there are prolonged bursts of motor unit potentials, firing at rapid rates of 150-300 Hz, which begin and end abruptly, do not occur repetitively in a rhythmic fashion and have a characteristic waning amplitude. There are few descriptions in companion animals but it appears to be an emerging problem in Jack Russell Terriers.

## Muscle cramps

This term describes prolonged and severe contraction of muscles that may be painful and can be either focal or generalized. Examples of diseases associated with cramps include 'Scotty cramp', 'episodic falling of Cavalier King Charles Spaniels', and muscle cramps secondary to hypoadrenocorticism. As these are paroxysmal syndromes they are described in full in Chapter 17.

#### **Lesion localization**

Tremor is ultimately a disorder of movement (Jankovic and Fahnn, 1980). Therefore, lesions in any region of the CNS, PNS and musculoskeletal system primarily responsible for normal movement, may generate a tremor. This makes localization challenging when considering the clinical signs alone (Figure 12.1). In humans, important motor areas include the basal nuclei and other components of the extrapyramidal system, the cerebellum, diffuse neuronal cell bodies involved in segmental and supraspinal reflex mechanisms, components of the lower motor neuron (LMN) and the interconnecting pathways. Additionally, abnormalities



Lesion localization for tremors; the central nervous system (including the cerebrum, cerebellum and the meninges) and the diffuse peripheral nervous tissue are highlighted.

of the mechanical apparatus of the limbs (e.g. bones, joints and tendons) may also result in tremor as a result of pain and weakness. However, species differences do exist and it is important to note that lesions involving the basal nuclei and substantia nigra commonly result in tremor in human beings but not in dogs (Adams and Victor, 1989).

Tremors that occur or worsen when an animal is trying to perform purposeful movements (intention tremor) are most often associated with cerebellar disease. Fine tremor (decreased amplitude and increased frequency) is more often associated with diffuse neuronal disease or muscle weakness. The causative lesion may give rise to other signs of neurological dysfunction that can help to define the localization, such as dysmetria associated with cerebellar disease.

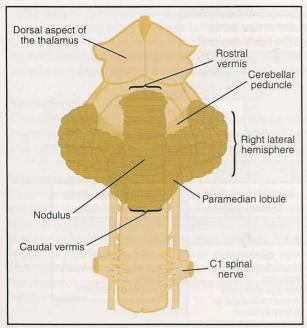
# **Pathophysiology**

#### Physiological tremor

Several hypotheses have been proposed to explain physiological tremor. Traditionally it has been thought to represent the passive vibration of body tissues produced by mechanical activity of cardiac origin. However, of greater significance is probably the contribution of spontaneous firing of groups of motor neurons and the natural resonating frequencies of muscle fibres. Certain abnormal tremors, especially the metabolic variety of action tremors, due for example to hypoglycaemia and phaeochromocytoma, are believed to be exaggerations of physiological tremor.

#### Cerebellar dysfunction

The cerebellum functions to control movement once movement has been initiated (deLahunta, 1983; Chrisman, 1986; King, 1987). The cerebellum also assists with regulation of posture, unconscious proprioception and muscle tone. Structurally, the cerebellum contains two lateral hemispheres primarily responsible for limb movements; a median portion or vermis, primarily responsible for regulating posture and muscle tone; and a ventral portion (the flocculonodular lobe), primarily responsible for the maintenance of equilibrium and coordination of head and eye movements (Figure 12.2). The cerebellar cortex in all regions is made up of the outer molecular layer, the middle Purkinje cell layer and the inner



Schematic dorsal view of the cerebellum, caudal brainstem and cranial cervical spinal cord.

granule cell layer (Figure 12.3). The cerebellar cortex has a predominant inhibitory influence on the three paired cerebellar nuclei of the subcortical white matter (fastigial, interposital and dentate) that are then responsible for the control, but not the initiation, of head and limb movements. Afferent and efferent information to and from the cerebellum is transmitted via three paired cerebellar peduncles attaching the cerebellum to the brainstem.

Signs of dysfunction in any area of the cerebellum usually include abnormalities of the rate, range, direction and force of motor movements. There are no signs

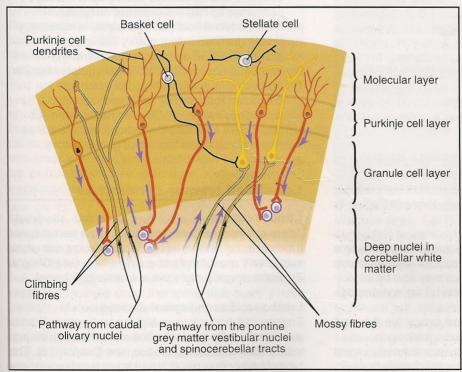
of weakness or paresis seen with 'pure' cerebellar dysfunction. Tremor seen with cerebellar disease is most obvious when the animal tries to make a goal-orientated effort and it is therefore referred to as an intention tremor. This type of tremor, which implies a lesion of the cerebellar hemispheres, often becomes more obvious when an animal attempts to lower its head to eat or drink. Intention tremors may involve the head or the entire body, and may be accompanied by other signs of cerebellar dysfunction such as ataxia and hypermetria.

# CNS and peripheral nerve dysfunction

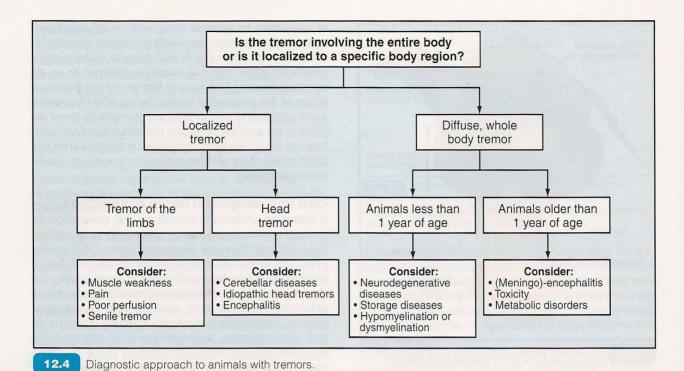
A common underlying theme to the generation of tremors or other involuntary movements is spontaneous neuronal or axonal discharges in the CNS and/or PNS. This increased excitability can be caused by any disorder that interferes with normal myelination, ion channel function, electrolyte concentrations (especially potassium, calcium and sodium) and neurotransmission. Inherited (e.g. dysmyelination in Chow Chows and Weimaraners), inflammatory and compressive disorders can all affect any one or more of these parameters producing tremors or other involuntary movements.

# **Differential diagnosis**

The differential diagnosis is based upon the type of tremor or involuntary movement present. Tremors tend to be localized or generalized, and categorizing movement disorders in this way helps to determine the list of differential diagnoses (Figure 12.4) (Bagley 1992). Intention tremor, being somewhat different, is most often associated with cerebellar diseases (deLahunta 1983).



Schematic magnification of the neuronal circuitry present in the cerebellum. The arrows indicate the direction of impulse transmission.



**Diagnosis** 

Obtaining an accurate history of the patient is important to define the onset and progression of the condition in addition to elucidating any underlying systemic health problems that could be causing the disorder. Important questions are listed in Figure 12.5.

# Important historical questions about the patient with tremors and involuntary movement disorders

Was the onset of the condition acute?

Has the condition been progressive?

Has the condition been constant or intermittent?

Do the tremors disappear during sleep?

If the animal is young, is there any information available about the littermates?

Is there any possibility of exposure to toxins?

What medications is the patient on?

Is the patient on a standard diet?

Have there been any recent changes in personality or behaviour?

Are there any recent changes with the patient's appetite or thirst?

12.5

Important questions to ask when establishing a diagnosis.

Complete physical examination is essential as some tremor disorders may be associated with systemic disease. Many tremor syndromes may also be associated with neurological deficits; therefore, a neurological examination can help to localize the causative lesion or associated deficits and determine the next stages necessary in the diagnostic work-up.

The following tests should be considered in most patients with tremors and movement disorders:

- Haematology, serum biochemistry analysis and urinalysis can help rule out systemic disease including hypoglycaemia, hypocalcaemia and other electrolyte abnormalities
- Testing for possible toxin exposure can be difficult without knowledge of which toxin to look for; serum cholinesterase activity can be dramatically lowered in cases of organophosphate toxicity; blood lead levels should be considered if there is a history of possible exposure
- Thoracic and abdominal radiographs should be performed to rule out systemic neoplasia
- Cerebrospinal fluid (CSF) analysis is necessary to rule out CNS inflammatory diseases
- Serum and CSF serology can confirm the infectious nature of a CNS inflammatory disease
- Advanced imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI) can help to rule out destructive inflammatory lesions in the CNS as well as focal mass lesions (e.g. neoplasia).

#### **Localized tremor syndromes**

#### **Limb tremors**

There are many different causes of limb tremors, and it should be remembered that focal seizures can cause involuntary movements of a single limb (see Chapter 7). Some specific diseases are described below.

#### Lumbar and sacral spinal disease

Tremor can occur in one limb or body area. Tremor restricted to only the pelvic limbs may be seen in dogs with lumbar and sacral disease (see Chapter 18). This type of tremor may result in part from muscle weakness

secondary to spinal cord or peripheral nerve impingement, or possibly occurs as a reflection of pain. Pelvic limb tremor may result from compressive diseases such as lumbosacral vertebral canal stenosis, neoplasia and discospondylitis (Bagley, 1992).

#### Senile tremor

Older dogs can have tremors of the pelvic limbs (senile tremor); however, the aetiology and pathogenesis of this syndrome remains unknown (Kornegay, 1986a).

#### Vascular diseases

Limb tremors may also be seen with poor perfusion to the limbs resulting from cardiac, pulmonary or vascular disease, or anaemia. Localized cyanosis secondary to a right-to-left shunting patent ductus arteriosus can result in pelvic limb tremor, most commonly seen during or following exercise. Partial vascular thrombosis and occlusion of the femoral arteries may result in similar tremor.

#### Neuromuscular diseases

Diseases associated with muscle weakness such as myopathy and myasthenia gravis may be associated with muscle tremors (see Chapter 17). Tremors associated with these diseases, however, are often of short duration, episodic and present during attempts at muscle activity.

#### Myoclonus

Myoclonus involving one limb is a relatively specific finding in canine spinal distemper infection (see Chapters 10 and 15). However, other inflammatory diseases have been associated with this clinical sign. Myoclonus is thought to be due to abnormal pacemaker activity in neurons damaged by the distemper infection.

#### Involuntary movements of the head

Dogs occasionally have tremor involving only the head (Bagley, 1992). This type of tremor most likely results from tremor of the neck muscles but its pathophysiology is poorly understood. Head tremors that are exacerbated by an intentional movement, such as eating or drinking, are termed intention tremors. This abnormality indicates cerebellar dysfunction (see Generalized tremors for specific diseases). Focal facial movement abnormalities or intermittent head movements and/or jerks should also be considered as potential seizure disorders and investigated appropriately (see Chapter 7).

## Metabolic, systemic and toxic diseases

Head tremors or bobs have been reported in a dog undergoing peritoneal dialysis for renal failure and in a dog with iatrogenic hypoparathyroidism. The author has seen dogs with a variety of systemic illnesses receiving multiple drug therapies that have similar tremors. Metoclopramide treatment and doxorubicin administration are notable examples. Additionally, a dog evaluated at the author's hospital with syncope due to third degree heart block had an intermittent affirmation head tremor.

#### Idiopathic head tremor (head bob)

Clinical signs: This head tremor syndrome appears to occur without definable cause in some breeds, such as the Dobermann Pinscher (especially dogs <1 year of age) and Bulldogs; however, a variety of breeds can be affected (Bagley, 1992; Kornegay, 1986a). These dogs have no other clinical abnormalities. Head tremors may be in either an up-down or a side-to-side plane. Sometimes this is referred to as a head bob. Head tremors are usually more prominent when the dog is less active. Also, dogs seem to be able to stop this movement if they desire. This is almost the opposite of an intention tremor, as the tremor can be stopped when the dog is focused on a goal-orientated task such as eating.

**Pathogenesis:** The pathogenesis of this disease is not known. In human beings a nodding of the head can occur with lesions of the thalamus. A head tremor in an anterior-posterior direction may also accompany midline cerebellar lesions.

**Diagnosis:** A full diagnostic work-up (blood work, CSF analysis and imaging of the brain) is normal.

**Treatment:** There is little information on the most appropriate treatment; although there may be a partial response to antiepileptic drugs, usually they are ineffective. Fortunately, these tremors rarely affect the animal's quality of life.

#### Infectious and inflammatory causes

Although unusual, animals with a head tremor or head bob as their only clinical sign can have an inflammatory or infectious disease (see Chapter 10). In addition, myoclonus of the head or face can be seen with inflammatory diseases of the CNS. An example are the 'chewing gum fits' so-called due to the rhythmic jaw movements seen clinically with canine distemper virus infections. However, it may be difficult to distinguish this form of localized myoclonus from continuous focal seizure activity. Focal facial movement abnormalities or intermittent head movements and/or jerks should always be considered as potential seizure disorders and investigated appropriately (see Chapter 7).

# **Generalized tremor syndromes**

Generalized tremors are surprisingly common in dogs (Farrow, 1986; Bagley, 1992; Bagley *et al.*, 1993; Wagner *et al.*, 1997). This type of tremor can occur secondary to intoxications, drug therapies, congenital myelin abnormalities, storage diseases, encephalitis, or may arise without a definable cause.

#### Degenerative diseases

#### Lysosomal storage diseases

Lysosomal storage diseases of the nervous system may have tremor as a presenting abnormality. Examples include globoid cell leucodystrophy, mannosidosis

and gangliosidosis. The numerous storage diseases and their associated characteristic clinical signs have been described elsewhere (Braund, 1987; March, 1996).

Clinical signs: These diseases are often breedrelated (see Appendix 1) with clinical signs first appearing in animals <1 year of age, but they can occur at any age. Many of these diseases involve the cerebellum and are associated with intention tremors.

**Pathogenesis:** Accumulation of metabolic byproducts within neurons or the surrounding neuropil usually results from an inherited deficiency of a specific catabolic enzyme. The accumulation causes dysfunction of the cells and regions of the nervous system affected.

**Diagnosis:** Ante-mortem testing for many of these diseases often results in negative or normal findings. CSF analysis is often normal, although occasionally inclusions can be seen in mononuclear cells (see Chapter 3). Advanced imaging tests may show signs of symmetrical anatomically defined pathology but the characteristics are not specific. Definitive diagnosis is often rendered only at necropsy and histopathological examination of the nervous tissue. However, there are specific blood and urine tests for many of these diseases that can be performed at specialist laboratories. For information on these tests the reader is referred to the Appendix 1.

**Treatment and prognosis:** Typically there is no effective treatment for affected animals, and clinical signs associated with degenerative diseases progressively worsen. Animals are commonly euthanized due to the progressive incapacitation.

#### Motor neuronopathies

Motor neuronopathies are degenerative diseases that affect the cell bodies of the LMN leading to degeneration of the cell in the ventral horn of the spinal cord and occasionally the cranial nerve nuclei (see Chapter 14 and Appendix 1 for specific breeds affected). Histological lesions are most severe in the ventral spinal grey matter and consist of neuronal cell loss and gliosis. Signs of motor neuronopathies include tremor, progressive weakness, cervical ventroflexion, dysphagia and muscle atrophy (Shelton *et al.*, 1998). As disease progresses, mild to moderate fibrillation potentials may be found in the appendicular and paraspinal muscles with electromyography. CSF analysis is normal as are imaging tests. There are no known treatments (see also Chapter 14).

# Feline encephalomyelopathy

An encephalomyelopathy of young cats has been reported in the UK (Palmer and Cavanagh, 1995). Wallerian degeneration was noted primarily involving the spinocerebellar pathways and the ventral funiculus of the spinal cord. A viral aetiology was suggested but not proven. Cats aged 3–12 months were affected; however, the disease was seen in cats up to 3 years of

age. Clinical signs were usually progressive over weeks to months. Signs included ataxia, paresis, and 'head shaking'. Ataxia of the pelvic limbs was the initial clinical sign noted.

#### Anomalous diseases

# Dysmyelination and hypomyelination

In this group of diseases the axons within the CNS may be thinly myelinated (hypomyelination), myelinated with abnormal myelin (dysmyelination) or may be unmyelinated.

Clinical signs: Many breeds of dog are affected by this group of congenital disorders of myelination including the Chow Chow, Springer Spaniel, Samoyed, Bernese Mountain Dog and Weimaraner. Signs are usually evident as soon as the animal starts to walk. Tremor in these animals affects the whole body and is classed as action tremor as it is usually worse with excitement or movement and stops during sleep. Some affected animals appear as though they are 'bouncing'. The severity of the tremor decreases with age in breeds of dog with dysmyelination (e.g. Chow Chow, Weimaraner).

Pathogenesis: Abnormal myelination of the CNS can affect nerve impulse conduction and cause tremor (deLahunta, 1983; Duncan, 1987). It is possible that altered impulse conduction or spontaneous discharge of unmyelinated axons (perhaps as a result of increased extracellular potassium concentrations) may generate the tremor. The degree of the tremor correlates with the severity of the myelin abnormality. The underlying cause is unknown but, as these diseases are believed to be inherited, a genetic defect of myelination is suspected (Duncan, 1987).

**Diagnosis:** A definitive diagnosis is reached only by histopathological evaluation of the CNS. The classic clinical presentation in young dogs of the correct breeds is very suggestive. However, infectious, inflammatory, systemic and toxic diseases should be ruled out.

Treatment and prognosis: There is no known treatment for this group of diseases. In breeds with dysmyelination, improvement will occur with age and the tremor may resolve when the animal becomes an adult and the myelin sheath reaches normal thickness.

#### Metabolic diseases

Alterations in the metabolic environment of muscles and nerves may result in alterations of muscle and nerve membrane resting potentials with subsequent spontaneous depolarization. Electrolyte (hypo- and hypercalcaemia and -natraemia), glucose and acid-base imbalances are the most common metabolic abnormalities resulting in tremor. Tremors and fasciculation, rather than muscle weakness, are more common with hypocalcaemia than with hypercalcaemia. Tremors and fasciculation with metabolic conditions tend to be episodic and of irregular frequency.

#### Hypocalcaemia

Clinical signs: The clinical signs include weakness, tetany and tremors. Spontaneous muscle depolarization can manifest as muscle fasciculation, cramping, rigidity and twitching. Signs can progress to include focal (e.g. ears or facial muscles) or generalized muscle tremors, seizures, weakness or ataxia.

**Pathogenesis:** Hypocalcaemia can result from iatrogenic injury to the parathyroid gland during surgical removal of thyroid tumours (especially in cats) and can be associated with lactation (eclampsia) (most commonly in dogs). Primary hypoparathyroidism is rare (Forbes *et al.*, 1990; Peterson *et al.*, 1991). Hypocalcaemia decreases the threshold for neuronal and muscle depolarization due to alterations in sodium flux and membrane potentials (Peterson *et al.*, 1991; Feldman and Nelson, 1996).

**Diagnosis:** The diagnosis is supported by finding decreased (usually <1.5 mmol/l (6 mg/dl)) total calcium on serum biochemical analysis.

Treatment and prognosis: Treatment involves calcium supplementation and vitamin D therapy. If clinical signs are present, rapid institution of treatment is indicated with 0.5–1.5 ml/kg i.v. of 10% calcium gluconate. Intravenous calcium should be administered slowly over 10 minutes while monitoring heart rate. Stop infusion if bradycardia occurs. Longer-term maintenance requires oral calcium (25 mg/kg q8–12h) and vitamin D supplementation. The active form of endogenous vitamin D3 (also called calcitriol or 1,25-dihydroxycholecalciferol) is used at 2.5–10 ng/kg q24h or synthetic vitamin D3 (dihydrotachysterol) at 0.02–0.03 mg/kg q24h for 3 days, then 0.01–0.02 mg/kg q6–24h.

Serum calcium concentrations should be monitored carefully as hypercalcaemia is nephrotoxic. Adjustments to doses should be made every 1–3 days based on calcium concentrations. If hypocalcaemia is the result of thyroidectomy, calcium and vitamin D therapy can be reduced gradually over 2–3 weeks and stopped if calcium remains in the normal range. Acute hypocalcaemia following bilateral thyroidectomy can be fatal if delayed recognition prevents early institution of an appropriate therapy.

#### Hypo- and hypernatraemia

Sodium salts represent the major osmotically active solutes in the body. Clinically, hyponatraemia is synonymous with hypo-osmolality, and hypernatraemia is synonymous with hyperosmolality. Neurological signs usually include changes in the level of awareness and seizure activity (see Chapter 8) but can include tremors.

#### Hypoglycaemia

Hypoglycaemia is more likely to cause changes in mentation, stupor, coma or seizures rather than tremors but it should always be considered as a differential (see Chapters 7 and 8). This is particularly relevant in dogs with insulinomas with an associated paraneoplastic peripheral neuropathy (see Chapter 14).

#### Hepatic encephalopathy

Liver dysfunction affecting the nervous system causes changes in mentation and seizure activity more often than tremors, but they may occur in association with the cerebral signs of disease (see Chapter 8).

#### Neoplastic diseases

Neoplastic disease of any area of the nervous system has the potential to cause tremors usually, but not always, in the presence of more specific signs referable to the location of the tumour.

# Inflammatory diseases

Generalized tremors without other definable systemic cause are most often secondary to inflammatory brain disease (Farrow, 1986; Bagley, 1992; Bagley *et al.*, 1993; Wagner *et al.*, 1997).

# Generalized tremor syndrome of dogs

Clinical signs: This condition was historically identified in small breed (<15 kg) dogs with white hair coats (for example, Maltese) hence these dogs were described as 'white shakers'. However, dogs with various other hair coat colours may be similarly affected (e.g. Miniature Pinschers), and therefore the term 'generalized tremor syndrome' is often used.

Affected dogs are usually <2 years of age when a generalized tremor begins. Early in the disease course owners may interpret the tremor as their animal being 'scared' or 'cold'. When tremors become more persistent owners then elect veterinary evaluation. Tremors in these dogs usually occur multiple times per second and are not associated with large to and fro movements. This low amplitude, relatively rapid tremor is sometimes described as 'fine'. Tremors worsen with excitement and improve with sleep. However, the author has evaluated two dogs with generalized tremors when awake that had a persistent thoracic limb myoclonus while under general anaesthesia. Other clinical signs may suggest a diffuse CNS problem, such as menace deficits, hypermetria, nystagmus, conscious proprioception deficits and seizures.

**Pathogenesis:** Generalized tremor syndrome is often associated with a mild degree of encephalitis. Histological examination of affected dogs revealed a mild, non-suppurative meningoencephalomyelitis in some. Not all dogs examined histologically have pathological changes in the CNS.

**Diagnosis:** The CSF from affected animals usually contains mild increases in nucleated cell counts and a normal to slightly elevated protein content. No obvious infectious or immune aetiology for the encephalitis has been identified.

**Treatment and prognosis:** Clinical signs usually respond to corticosteroids (prednisolone 1–2 mg/kg q12h). This dose is administered for 1–2 weeks or until clinical signs are resolved. After the clinical signs have initially

resolved, the corticosteroid dosage can be slowly decreased (over weeks to months) to prevent recurrence. Too rapid a reduction in the corticosteroid dose can result in recurrence of clinical signs. The disease in some dogs will remain in remission only with continual corticosteroid administration similar to other autoimmune diseases. Some dogs will never show 100% improvement and some dogs will relapse at the end of steroid treatment or with dose reduction; relapse has been reported to be associated with vaccination in some dogs but repeat treatment has been documented as effective. Other drugs used in human beings for the treatment of this cause of tremor such as propranolol (0.5-1.0 mg/kg orally q8h), diazepam (0.5-1 mg/kg orally q8h) and phenobarbital (2-4 mg/kg orally q12h) either have been used too infrequently to assess therapeutic response, or are not effective at controlling generalized tremor in dogs.

#### **Encephalomyelitis in cats**

Encephalomyelitis is a much more infrequent cause of tremor in cats than in dogs.

Clinical signs: Any age of cat may be affected. Diffuse, whole-body low amplitude (fine), higher frequency tremor is present. Cats may also twitch periodically. Other neurological signs that may be present in cats with encephalomyelitis include seizures, blindness, conscious proprioceptive deficits and cranial nerve deficits. Neurological signs may not localize to a single area within the nervous system.

**Pathogenesis:** As for the canine syndrome discussed above, there may be an unknown or poorly defined cause of CNS inflammation that may cause tremors as one of its signs. The underlying pathogenesis of these generalized tremors is poorly understood.

Diagnosis: CSF may contain increased numbers of nucleated cells and/or elevated protein concentrations. Nucleated cell counts can vary from mild (5–20 cell/μl; normal <2–5 cells/μl) to moderately elevated (>50 cells/μl; normal <2–5 cells). The nucleated cell type is variable but most often is a mononuclear cell population. Neutrophils may also be seen. This syndrome is associated with histological evidence of inflammation of the CNS. However, a consistent infectious aetiology has not been identified.

**Treatment and prognosis:** Treatment with corticosteroids (prednisolone 2 mg/kg q12h initially) may improve clinical signs. If clinical signs improve, the corticosteroid therapy should be slowly tapered (over months) to prevent recurrence. Poor response or relapse may be frequent.

#### Polioencephalomyelitis

Young to middle-aged cats have been diagnosed with tremors due to polioencephalomyelitis (Vandevelde and Braund, 1979).

Clinical signs: Affected cats described had a slow chronically progressive onset with signs including pel-

vic limb ataxia, seizures, paresis, hypermetria, intention tremors, decreased pupillary light reflexes and hyperaesthesia over the thoracolumbar area. Seizures were noted during sleep and were characterized by staring, clawing, biting and hissing. CSF from one cat contained elevated protein.

**Pathogenesis:** Lesions primarily occur in the spinal cord and include severe degeneration and loss of neurons, perivascular mononuclear cuffing, lymphocytic meningitis, neuronphagia and glial nodules. A viral aetiology was suggested but not proved.

*Diagnosis:* CSF fluid may contain an elevated protein content but any changes in cell count or protein levels are non-specific. MRI scans may reveal a non-specific pattern of multifocal inflammatory change. Definitive diagnosis is often only made at necropsy. Histological lesions are most severe in the spinal cord and include severe degeneration and loss of neurons, perivascular mononuclear cuffing, lymphocytic meningitis, neuronophagia and glial nodules.

**Treatment and prognosis:** No treatment is known or has been attempted. Clinical signs are progressive up until euthanasia.

#### Feline spongiform encephalopathy

A spongiform encephalopathy occurs in older cats in the UK and a prion protein may be the cause (Leggett et al., 1990) although this disease has now not been reported in the last 5 years. Spongiform encephalopathy occurs in older cats and clinical signs include muscle tremors, ataxia, dilated unresponsive pupils, jaw champing, salivation and behaviour abnormalities.

#### Idiopathic diseases

#### Feline hyperaesthesia syndrome

Clinical signs: Feline hyperaesthesia syndrome is a unique disease that may result in episodic muscle twitching and fasciculation (deLahunta, 1983). Cats may become agitated and aggressive, show skin rippling and muscle spasms, usually in the lumbar area with stimulation (such as stroking) over the thoracolumbar region. Cats may seem startled and then exhibit frenzied behaviour, such as licking or biting at the flanks, back and tail, or running. Cats may appear as though they are hallucinating and have dilated pupils. Sudden startling, running, frantic meowing, growling, hissing and swishing of the tail may also occur. Episodes may occur many times in a day and last from 1 to 5 minutes.

**Pathogenesis:** The cause of this syndrome is unknown. One theory suggests that this activity is a manifestation of a focal seizure. Another theory suggests that it is similar to the obsessive—compulsive behaviour associated with Tourette's syndrome in humans, which is the result of dopaminergic hyperinnervation. Similar clinical signs have been associated with a vacuolar myopathy in cats and

toxoplasmosis. Others have suggested that this may be a primary behavioural disorder. Some believe that in the majority of cats it begins with an inflammatory stimulus, such as flea or food allergy dermatitis.

**Diagnosis:** The diagnosis is usually made solely on clinical signs and by ruling out underlying diseases, such as dermatitis, lumbosacral spinal cord or nerve root compression and intracranial disease. It is important to determine whether this is simply behaviour associated with oestrus.

Treatment and prognosis: Initial treatment should be with anti-inflammatory drugs. Corticosteroid therapy (prednisolone) may help if a flea allergy or other inflammatory stimulus is suspected. Non-steroidal antiinflammatory drugs (e.g. piroxicam, meloxicam) or megoestrol acetate can also be tried. Strict flea control may improve clinical signs. Behaviour-modifying drugs, such as the tricyclic antidepressants amitriptyline (2 mg/kg or 5-10 mg/cat orally q24h), clomipramine (1-5 mg/cat orally q12-24h) or the selective serotonin uptake inhibitors fluoxetine (0.5-4 mg/cat orally g24h) or paroxetine (0.5 mg/kg orally q24h) may be helpful in some cats. Anticonvulsants (phenobarbital beginning at 3 mg/kg orally q12h with dose adjustments to maintain trough serum levels at 20-40 µg/ml) may help if anti-inflammatory and behaviour-modifying drugs are unsuccessful. Feeding food without preservatives has been suggested as helpful. Carnitine/Co-enzyme Q<sub>10</sub> may help cats with vacuolar myopathy, and antioxidants and omega-3 fatty acids may also be useful (see Chapter 17). It may be important to decrease environ-

Prognosis can depend on the identification of an underlying disease and initial response of the animal to medication as well as the frequency and severity of these events.

#### Reflex myoclonus

Clinical signs: This rare disease is characterized by episodic, stimulation-evoked extensor rigidity of the body. It has been reported in Labrador Retrievers (Fox et al., 1984; March et al., 1993) with onset of progressive signs around 12 weeks of age. Affected animals become stiff, usually when excited or stimulated, and the signs become so severe that the animal is unable to walk or even stand. Other breeds (e.g. Dalmatian) are occasionally affected.

**Pathogenesis:** This appears to be a familial disorder in Labrador Retrievers. The pathogenesis is unknown but it is thought that there is a loss of inhibitory neurotransmission at the level of the spinal cord.

**Diagnosis:** The diagnosis is by recognition of the typical clinical signs and EMG, which reveals bursts of giant polyphasic motor units.

**Treatment and prognosis:** Although the extensor rigidity is partially responsive to diazepam and phenobarbital, resolution of signs is unlikely and the prognosis is poor.

#### Toxic diseases

Some acute toxicities may result in tremor (Dorman, 1993; Dorman and Fikes, 1993).

#### Clinical signs

Tremor is possible with multiple intoxications including organophosphate, hexachlorophene and bromethalin toxicity. Metaldehyde and strychnine usually cause tetany and seizures; however, tremor may also be seen. Mycotoxins, such as penitrem-A, have been associated with tremor in dogs (deLahunta, 1983; Wagner *et al.*, 1997). Ivermectin toxicosis has resulted in generalized ataxia, tremor, weakness, incoordination and miosis in both cats and dogs. Other toxicities that result in nervous system stimulation, such as chocolate, amphetamines and caffeine, may have tremors as an associated clinical sign.

#### **Pathogenesis**

The generating mechanism of tremor with many of these toxic substances is not known. Toxins may lower the threshold for stimulation or directly stimulate muscles and nerves to result in tremor. Organophosphate intoxication potentiates the effect of acetylcholine (ACh) at the neuromuscular junction and other synapses by binding with and inactivating acetylcholinesterase. This leads to increased ACh concentrations at the neuromuscular junction, increased receptor stimulation and fatigue. Pathological alterations in the nervous system, for example intramyelinic oedema caused by agents such as hexachlorophene and bromethalin, could possibly alter nerve impulse conduction to result in tremor. Other substances most likely result in imbalances in neurotransmitter concentrations as a tremor-producing mechanism. Ivermectin increases the effects of gamma-aminobutyric acid (GABA; inhibitory neurotransmitter) in the CNS.

Numerous drug therapies may cause tremor as a side-effect, possibly through alterations in the normal function of the extrapyramidal system and alterations in the balance of normal neurotransmitter levels. Examples include fentanyl and/or droperidol, epinephrine (adrenaline), isoproterenol and 5-flurouracil (Bagley, 1992).

#### Diagnosis

History of exposure to a toxic product is most helpful in establishing a diagnosis. Specific blood testing may be possible in these cases. For organophosphate toxicity, decreased concentration of serum cholinesterase activity (<25% of the normal) may lend support to the diagnosis. Depending upon the laboratory, values <500 IU/I (normal 900–1200 IU/I) are considered compatible with organophosphate toxicity.

#### Treatment and prognosis

For organophosphate toxicity treatment includes protopam or pralidoxime chloride (2-PAM) (20 mg/kg i.m. q12h), which reactivates cholinesterase and diphenhydramine (1–2 mg/kg orally q8–12h) to reduce muscle fasciculation. These medications should be repeated until signs are abolished or until additional benefit is no longer observed; enzyme reactivators, such as

protopam, may not be effective after 24 hours of exposure as they are only helpful if covalent binding of the insecticide to acetylcholinesterase has not yet occurred. Atropine sulphate (0.2-0.4 mg/kg) can be given with acute toxicity to decrease muscarinic autonomic signs but it will not abolish the muscle tremors due to excessive nicotinic stimulation. Current recommendations are that it should be used only if marked bradycardia is present as atropine may precipitate respiratory arrest. Salivation and defecation are not life-threatening and generally do not require atropine. Diazepam should be avoided in cats with organophosphate toxicity as it may result in generalized muscle tremor, hypersalivation, miotic pupils and vomiting similar to the acute muscarinic signs of organophosphate toxicosis (Jaggy and Oliver, 1990).

It is important to avoid further exposures to organophosphates until the animal is clinically recovered. No specific antidote exists for the other toxicities described here but general supportive measures for toxin exposure should be pursued. Prognosis is variable dependent on the specific toxin.

# Intention tremors due to cerebellar disorders

Tremors that occur when an animal intends to move in a goal-orientated activity are most often the result of cerebellar disease (deLahunta, 1983).

# Degenerative diseases

#### Cerebellar cortical degeneration

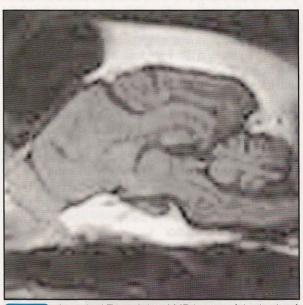
Cerebellar cortical degeneration, also termed cerebellar abiotrophy, is usually an inherited disease in dogs (deLahunta, 1980) with few reports in cats. Primary cerebellar cortical degeneration refers to degeneration and loss of Purkinje cells, molecular cells and granule cells.

Clinical signs: These diseases are recognized syndromes in American Staffordshire Terriers, American Pit Bull Terriers, Kerry Blue Terriers, Gordon Setters, Rough-coated Collies, Border Collies, Brittany Spaniels, Bullmastiffs, Old English Sheepdogs and occur rarely in Samoyeds, Airedales, Finnish Harriers, Labrador Retrievers, Golden Retrievers, Beagles, Cocker Spaniels, Cairn Terriers, Great Danes, Scottish Terriers and others (deLahunta, 1980).

Clinical signs usually begin between 3 and 12 months of age. However, a subset of adult onset diseases occur with signs starting from 2–8 years of age in the Brittany Spaniel (Higgins et al., 1998), Gordon Setter (deLahunta et al., 1980), Old English Sheepdog (Steinberg et al., 2000), American Staffordshire Terrier (Olby et al., 2004) and Scottish Terrier (van der Merwe et al., 2001). Other signs of cerebellar disease that accompany cerebellar tremor include ataxia, dysmetria, menace deficits, head tilt, nystagmus (Holliday, 1979/1980; deLahunta, 1983), truncal sway and infrequently anisocoria. Clinical signs associated with degenerative cerebellar diseases progressively worsen.

Pathogenesis: Abiotrophy is a process by which cells develop normally but later degenerate because of an intrinsic cellular defect necessary for continued life of the neuron (deLahunta, 1983). Many of these diseases may result from underlying abnormalities of cellular metabolism or cellular function (such as calcium and potassium channelopathies) and they are known to be inherited in American Staffordshire Terriers, Old English Sheepdogs, Gordon Setters and Brittany Spaniels.

*Diagnosis:* Ante-mortem testing for these diseases often results in negative or normal findings. Definitive diagnosis is usually rendered only at necropsy and histopathological examination of the nervous tissue. In some instances of cerebellar atrophy a smaller than normal cerebellum may be seen on MR imaging of the intracranial nervous system (Figure 12.6). This is most readily seen on the sagittal view. CSF with these degenerative cerebellar conditions is normal.



A sagittal T1-weighted MR image of the brain of a 6-year-old male castrated American Staffordshire Terrier with cortical degeneration. The cerebellar folia are clearly visible as a result of the CSF lying between them reflecting the cerebellar atrophy.

**Treatment and prognosis:** There are no effective treatments for this group of disorders and the prognosis is guarded to grave.

# Storage diseases

Storage diseases can result in cerebellar degeneration (Braund, 1987; March, 1996). These are discussed above and are listed in Appendix 1. Cellular products accumulate and affect neuronal cells physiologically or mechanically resulting in cellular dysfunction, and hence, clinical signs. Clinical signs are of a progressive cerebellar disease. Diagnosis is based upon biopsy or necropsy. No treatment is effective. Breed specificities are documented in Appendix 1.



# Chapter 12 Tremor and involuntary movements

#### Neuroaxonal dystrophy

Clinical signs: This is a disease of Rottweiler dogs (Chrisman, 1986) but is also reported in Collies, Chihuahuas, Boxers, German Shepherd Dogs, Siamese and a family of domestic cats. In Rottweilers neuro-axonal dystrophy is characterized by cerebellar signs (ataxia, hypermetria, loss of menace, head tremor) beginning at 1–2 years (ataxia) and progressing over the next 2–4 years (menace deficits, intention tremor). Conscious proprioception remains intact.

**Pathogenesis:** The underlying pathogenesis is unknown. The cell bodies in the grey matter are affected (axonal spheroids) throughout the nervous system except the cerebral cortex. The most severe lesions are in the spinocerebellar tracts and the Purkinje cells.

Diagnosis: The diagnosis is usually established at post-mortem; however, ante-mortem biopsy of these areas may show pathological changes. Recognition of the characteristic clinical signs in young Rottweilers is suggestive of this disease, but a full diagnostic work-up (imaging and CSF analysis) is needed to rule out diseases that may be treatable (e.g. encephalitis). It is important to note that Rottweilers also suffer from a neurodegenerative disease called leucoencephalopathy, which causes progressive tetraparesis in young (1–4-year-old) Rottweilers (Chrisman, 1986). Younger Rottweilers (3–8 months) can develop a disease called neuronal vacuolation, which causes a combination of laryngeal paralysis, progressive tetraparesis and microphthalmia (Kortz et al., 1997).

**Treatment and prognosis:** No treatment is known and the long-term prognosis is poor.

#### **Anomalous diseases**

Congenital malformations of the cerebellum are occasionally seen. These include aplasia (an absence of cerebellar tissue) and partial agenesis or hypoplasia (partial or uniform lack of cerebellar tissue). Cerebellar hypoplasia has been associated with infection or toxin exposure during a critical stage of cerebellum development in-utero. Caudal vermian hypoplasia is described in some dogs with associated ventricular dilation (Dandy Walker-like malformation) (Kornegay, 1986b). Cerebellar hypoplasia has been recognized in Chow Chows, Irish Setters and Wire-haired Fox Terriers. The latter two breeds may have concurrent lissencephaly. Cerebellar aplasia has been reported in Siberian Huskies. Herniation of the cerebellar tonsils is a component of Chiari-like malformations that have been reported in various small breed dogs but in particular in Cavalier King Charles Spaniels (see Chapters 13 and 14).

#### Feline cerebellar hypoplasia

*Clinical signs:* Clinical signs are most apparent when the animal begins purposeful movement and attempts to walk. Tremor accompanying the disease usually has

a slower frequency (2–6 times per second) and larger amplitude. The tremor worsens (increases in frequency or amplitude) when the cat moves in a goal-oriented way (e.g. bends down to eat). Other signs include ataxia, hypermetria, menace deficits, head tilt and nystagmus. Clinical signs usually remain static or improve with growth as the cat compensates, causing the tremor to become less apparent.

Pathogenesis: Feline cerebellar hypoplasia is caused by in-utero infection with the panleucopenia virus (parvovirus), which affects the external germinal layer of the cerebellum and prevents the formation of the granular layer (deLahunta, 1983). Some affected cats have concurrent hydrocephalus and hydranencephaly. Infection of the fetus may occur when a pregnant queen is inoculated with a modified-live panleucopenia virus vaccination, which also destroys the external germinal layer of the cerebellum and prevents the formation of the granular layer.

*Diagnosis:* Ante-mortem testing for this disease often results in negative or normal findings. Occasionally, inflammatory cells may be present upon CSF examination in cats with active panleucopenia viral infection. CSF with the other degenerative cerebellar conditions and with non-active panleucopenia infection is usually normal. MRI evaluation can confirm the presence of a small cerebellum but it is not specific for this disease.

**Treatment and prognosis:** There is no treatment for this disorder. Some cases are mild but others can be quite severe, and in these cases walking and eating may be very difficult. As the signs do not progress with time the prognosis may be fair if the animal is only mildly affected. As prevention, it is important not to inoculate queens with a modified-live panleucopenia virus vaccine.

#### Neonatal ataxia in Coton de Tulear dogs

Clinical signs: Clinical signs become evident at 2 weeks of age once the puppies start to move around (Coates et al., 2002). They include head and intention tremors, severe ataxia and vertical nystagmus. The signs are not progressive but are so severe that most dogs cannot walk and are euthanized.

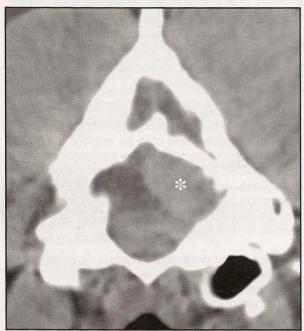
**Pathogenesis:** This is currently unknown but the disease is suspected to be an autosomal recessive disease that causes abnormal cerebellar development.

**Diagnosis:** The diagnosis is by recognition of the clinical signs and ruling out other possible causes. Histopathological findings may be minimal using light microscopy but electron microscopy reveals synaptic abnormalities.

**Treatment and prognosis:** There is no effective treatment at this time. Although the disease is not progressive the signs are so severe that the prognosis is grave.

## **Neoplastic diseases**

Primary or secondary neoplasia involving the cerebellum is uncommon. More common is primary neoplasia of the infratentorial region that may affect the cerebellum and includes meningioma and choroid plexus tumours. These tumours arise from the meninges and the choroid plexus of the fourth ventricle, respectively. Gliomas and medulloblastomas rarely involve the cerebellum in dogs. Other mass lesions such as dermoid and epidermoid cysts may arise within or around the fourth ventricle and compress the cerebellum. Diagnosis is afforded with advanced imaging studies such as MR or CT (Figure 12.7). See Chapter 8 for a full discussion of the treatment of brain tumours.



A transverse contrast-enhanced CT scan of the caudal fossa of a 10-year-old female spayed Boxer. There is a contrast-enhancing mass (\*) compressing the dorsal cerebellum. This was removed surgically and confirmed to be a meningioma.

#### Inflammatory diseases

The cerebellum can be involved with the same infectious and immune-mediated processes that result in encephalitis (Meric, 1986; Muñana, 1996). See Chapter 10 for a full description of these diseases. The cerebellum may also be affected by inflammation with the generalized tremor syndrome in dogs, described previously, and indeed this syndrome has been called idiopathic cerebellitis by some authors. No definitive cause for this inflammation has been elucidated.

# Presumed immune-mediated cerebellar granuloprival degeneration in Coton de Tulear dogs

*Clinical signs:* In this unusual disease of male Coton de Tulear dogs, onset of progressive cerebellar signs was noted at 8 weeks of age (Tipold et al., 2000).

**Pathogenesis:** Clusters of T lymphocytes were identified in the cerebellar cortex leading to the proposal

that this disease results from a genetically determined immune reaction against the granule cells.

**Diagnosis:** The diagnosis is obtained by histopathological evaluation of the brain post-mortem.

*Treatment and prognosis:* No treatment has been reported. Prognosis is grave.

# **Toxic diseases**

With the exception of metronidazole, toxicity rarely specifically affects the cerebellum but cerebellar dysfunction may be part of the clinical syndrome of many toxin exposures. (See section above on the aetiology of tremors.)

#### Metronidazole toxicity

Toxicity with metronidazole may result in central vestibular and cerebellar signs in both dogs and cats (see Chapter 10). This can be associated with doses as low as 30 mg/kg/day. As metronidazole is metabolized by the liver, toxic serum levels can occur with lower doses in animals with liver dysfunction. Ataxia is usually the initial clinical sign, progressing to nystagmus and more severe vestibular and cerebellar dysfunction. Clinical signs often reflect central vestibular dysfunction and morphological lesions have been found in the brainstem of affected animals (see Chapter 10).

## Vascular diseases

Thromboembolic and vascular disease can involve the cerebellum (Bagley *et al.*, 1988; Berg and Joseph, 2003). Clinical signs often occur acutely, and rarely cause tremors alone (see Chapter 8).

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# **Neck and back pain**

# Simon R. Platt

#### Introduction

- Pain is a perception rather than a quantifiable entity resulting from a noxious stimulus.
- Hyperaesthesia describes an increased sensitivity to a normal level of stimulation, noted by the behavioural reaction of an animal; this is commonly seen when the animal's spine is palpated during a physical examination.
- *Hyperpathia* is the behavioural response to an injurious or noxious stimulation.

Many diseases encountered in veterinary medicine cause spinal pain, including multiple neurological diseases, as well as non-neurological diseases such as polyarthritis. Lesion localization is very important in cases of spinal pain, in order to ensure that the correct diagnostics are performed. In addition, interpretation of test results will only be possible with the knowledge of the results of the neurological examination. The treatment of spinal pain must be addressed both by treating the underlying disease and through the pharmacological alleviation of discomfort (see Chapter 20).

# **Clinical signs**

Recognition of the signs of spinal pain in animals can be made difficult by the variable reaction to pain seen between individuals. Some animals may give no outward indication that they are in pain, but there are several clinical signs that may be present and are useful for determining the presence of neck and back pain (Figure 13.1). Neck pain can be intermittent because of the dynamic nature of the cervical spine. In these cases, an accurate history in addition to video recordings of the episodes can be very helpful.

#### **Lesion localization**

Lesion localization is shown in Figure 13.2.

Spinal pain may result from disease of any of the numerous structures in the vertebral column, including: the meninges over the spinal cord and nerve roots; the nerve roots themselves; the annulus of the interver-

Decreased general activity levels

Depressed mentation

Change in normal attitude (i.e. aggression, withdrawal) and unexplained vocalization

Ventroflexion of neck

Stiff neck posture

Increased cervical muscle tone

Intermittent jerks or spasms of neck related to movement

Pain on palpation of vertebrae and spinal musculature

Pain on dorsal and lateral flexion of the cervical vertebrae

Gait abnormality: thoracic limb lameness (nerve root signature); stilted gait; stiff limbs; paresis if concurrent spinal cord disease

Historical reluctance to go up and down stairs, to climb into a vehicle or on to furniture, or to jump up

Historical observation of difficulty to get into resting position; may seem restless

Autonomic signs (e.g. salivation, increased respiratory and heart rates, pupillary dilation)

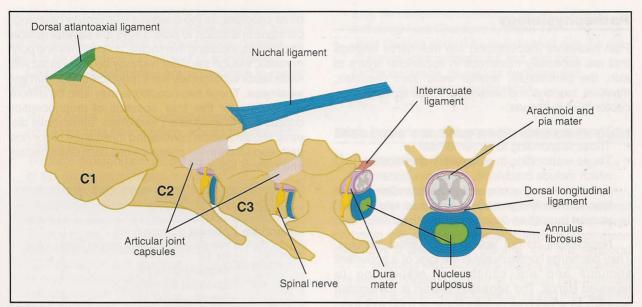
Unwillingness or inability to drink or eat from bowls on the floor

13.1

Clinical signs associated with neck or back pain.

tebral discs; vertebral periosteum; joint capsules (especially those of the diarthrodial joints of the articular processes); the epaxial musculature; and the ligamentous structures surrounding the vertebrae. It should also be noted that intracranial disease may cause a 'referred' type of neck pain, in circumstances or diseases where there is an elevated intracranial pressure that may cause compression or stretching of the cerebral vasculature and meninges, which are densely innervated with nociceptors.

Localization of painful areas is accomplished by a combination of historical evidence, observation (Figure 13.3), palpation and manipulation. After looking for the changes listed in Figure 13.1, the clinician must systematically palpate the animal, paying special attention to appendicular muscle bellies and appendicular joints. It is usually best to start caudally and work cranially to localize the pain. The vertebral column is palpated by pressing on the spinous processes or squeezing the articular or transverse processes, depending on the size and temperament of the animal (Figure 13.4a). Evaluation of the neck should also include flexion, extension and turning of the head and neck, with the palm of the hand placed on the side of the neck to evaluate any resistance to movement.



There are multiple origins of spinal pain, most of which are depicted here; they include ligaments, bone, nerve roots and spinal nerves, meninges, disc material and articular joints.

If possible, the pain should be localized to the cranial, middle or caudal cervical segments. When palpating the thoracolumbar spine to rule out diffuse spinal pain, a hand should be placed on the abdomen to detect increased tension in the muscles as painful areas are approached (Figure 13.4b). Pressing on the ribs may also be helpful in detecting thoracic vertebral pain. A few animals will be in so much pain that localization is impossible. Palpation of the head, temporal muscles and mandible, and opening the mouth are important in assessing cranial structures (see Chapter 1), and manipulation of the tail and the hips are important in assessing lumbar and lumbosacral structures (see Chapter 18).



A 9-year-old Schnauzer demonstrates severe neck pain with a stiff and flexed neck posture accompanied by poor weight bearing on the left thoracic limb, sometimes referred to as 'nerve root signature'.





Vertebral palpation. (a) Palpation of the cervical vertebrae can be accomplished with one hand in small dogs. Pain may be exhibited by an increase in muscle tone associated with the palpation, vocalization or a caudal 'flicking' of the ears. (b) Palpation of the thoracolumbar vertebrae should be performed with one hand underneath the abdomen of the patient, so as to detect any increase in muscle tone in this region associated with the palpation of a painful region. However, pain again may be noted by vocalization or turning around toward the examiner.

# **Pathophysiology**

Pain receptors (nociceptors) are free nerve endings that are especially numerous in superficial layers of skin, the periosteum, arterial walls, joint capsules, muscles, tendons and meninges. Three types of nociceptor exist in tissues:

- Those responding to excessive mechanical stress
- · Those responding to extreme heat
- Those responding to stimulatory chemicals, which include bradykinin, serotonin, histamine, potassium ions, acids, and prostaglandins, leucotrienes and proteolytic enzymes released in various quantities during inflammation.

Nociceptors do not 'adapt' to the initial stimulus. They discharge continuously in the face of a persistent stimulus and are capable of responding to repeated stimuli. The sensation of pain is transmitted centrally by small type A-delta fibres at 6–30 m/s (perceived as a sharp or pricking sensation), and by type C fibres at 0.5–2.0 m/s (perceived as a slow burning sensation); both of these types of pain can be felt at the same time. The conscious recognition of these sensations is due to their transmission up the multisynaptic and bilateral spinothalamic and spinoreticular tracts. These tracts pass to the pontobulbar reticular system with ongoing pathways to the thalamus, hypothalamus, and the mesencephalic areas, which reinforce the 'emotional' aspects of pain in humans.

Tissue damage or inflammation produces pain through stimulation of mechanosensitive, thermosensitive and chemosensitive nociceptors. The presence and intensity of pain are dependent on two variables:

- The presence of nociceptors (the central nervous system (CNS) does not have nociceptors, so damage to grey and white matter is not painful if other structures are not involved)
- The density of nocieptors. The meninges have a high density of nociceptors and are a source of spinal pain.

Occasionally, damage to the CNS can produce pain indirectly as a result of muscle spasm, which stimulates mechanosensitive nociceptors, and so pain relief must be directed toward muscle relaxation.

Unlike back pain, neck pain can commonly be present in the absence of any neurological signs; this is due to a lower spinal cord-to-vertebral canal diameter ratio, which allows for space-occupying lesions to irritate the cord and nerve roots without compressing them (Drost et al., 2002). There is a difference between dog breeds, with small breeds having a higher cervical cord-to-canal ratio than large breeds, meaning that small breeds would be more likely to have concurrent neurological signs and neck pain (Fourie and Kirberger, 1999).

#### **Differential diagnosis**

The diseases that frequently cause spinal pain are listed in Figure 13.5. Many of these are discussed in

other chapters, as the diseases often cause neurological signs in addition to pain. There are several notable exceptions, including meningitis, polyarthritis and polymyositis, though the latter two may be associated with weak flexor withdrawals due to physical discomfort and weakness. These two conditions may also be difficult to evaluate for the 'true' absence of proprioception deficits due to associated weakness. Intracranial disease should also be considered as a cause of cervical pain, especially in the presence of a compatible history and clinical signs.

Disease process	Specific diseases
Degenerative	Calcinosis circumscripta [14] Intervertebral disc disease (Hansen Types I, II & III) [14, 15] Wobbler syndrome [14] Spondylosis deformans [13] Synovial cysts [14]
Anomalous	Atlantoaxial instability [14] Chiari-like malformations Dermoid sinus [15] Osteochondromatosis [15] Perineurial (Tarlov) cysts [13] Scoliosis/Vertebral anomalies [15] Syringohydromyelia [14]
Neoplastic	Extradural [15]: Metastasis; vertebral tumours (sarcomas, plasma cell tumours); lymphoma Intradural/extramedullary: Meningiomas [15]; nerve sheath tumours [16]; metastasis [15] Intramedullary [15]: Ependymomas; gliomas; metastasis; round cell tumours. Less likely to cause pain Brain tumours: Primary or secondary with increased intracranial pressure [8]
Nutritional	Hypervitaminosis A [13]
Idiopathic	Arachnoid cysts [14]
Inflammatory	Infectious meningitis/meningomyelitis [10] Steroid-responsive meningitis-arteritis [13] Granulomatous meningoencephalomyelitis [10] Discospondylitis/osteomyelitis [13]; physitis [15] Empyema [14] Polyarthritis Polymyositis [17]
Trauma	Fractures/luxations [14,15,19] Spinal cord contusions [14,19] Traumatic disc herniations [14]
Vascular	Spinal/epidural haemorrhages [14]

Causes of neck and back pain. Numbers in brackets refer to chapters in which diseases are discussed further.

#### **Neurodiagnostic investigation**

The approach and subsequent tests required to 'work-up' the patient with spinal pain will depend on the history, clinical signs, physical and neurological examinations and, ultimately, the lesion or even system

localization. A general algorithm is shown in Figure 13.6. Polymyopathies, polyarthritides and soft tissue abnormalities, in addition to neurological disease, all need to be considered as causes of spinal pain.

Certain diagnostic tests are appropriate in cases with spinal pain:

- For all cases, initial clinicopathological tests should include haematology, serum biochemistry and urinalysis
- Thoracic radiographs should be obtained as part of the minimum database in dogs or cats with spinal pain; this is especially necessary in older animals and those in which cardiorespiratory disease is also suspected
- Survey spinal radiography is essential if a neurological disease is suspected
- CSF collection and analysis is essential when survey radiographs are normal, to rule out meningitis (see Chapter 3)
- Myelography, plain and contrast enhanced CT imaging or MR imaging are often necessary to evaluate patients with spinal pain if the above tests do not establish a diagnosis, especially if surgery is a consideration
- Muscle disease will need systemic investigation: electrophysiological testing and muscle biopsy

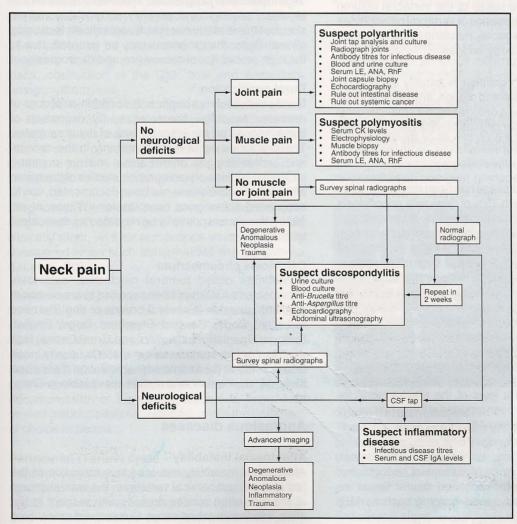
- may be needed to determine the underlying aetiology (see Chapters 4, 6 and 17)
- Joint disease should be investigated with the aid of survey joint radiographs and joint taps (arthrocentesis), as well as systemic and infectious disease investigations.

# Diseases causing neck and back pain

# Degenerative diseases

#### Intervertebral disc disease

Spinal cord compression secondary to intervertebral disc protrusion or extrusion is one of the most common clinical neurological disorders. Protrusion describes a disc that is 'bulging' into the vertebral canal, whereas extrusion describes a situation where the central nuclear material of the disc has ruptured through the dorsal fibrous structures into the vertebral canal. Acute (type I) cervical disc herniations commonly cause pain, which may be manifested as a 'nerve root signature', without obvious neurological deficits; the severity of the pain may be such that surgery is required. The pathophysiology, diagnosis and treatment of disc disease are discussed in Chapters 14 and 15.



clinical approach to neck pain. ANA = anti-nuclear antibody; CK = creatine kinase; CSF = cerebrospinal fluid; LE = lupus erythematosus; RhF = rheumatoid factor.

# Cervical stenotic myelopathy (Wobbler syndrome)

Also termed caudal cervical spondylomyelopathy, cervical spondylopathy, cervical spondylolisthesis, cervical malformation/malarticulation and disc-associated wobbler disease, this disorder most commonly affects Dobermann Pinschers and Great Danes, but many other breeds have been recognized with similar abnormalities. The age of onset of the disease is variable, ranging from 3 months to 9 years. Neck pain may be the only clinical sign of the disease; however, pelvic limb ataxia, pelvic limb paresis and ambulatory tetraparesis are commonly associated with the discomfort. For a complete discussion of the pathophysiology, diagnosis and treatment of this disease, the reader is directed to Chapter 14.

#### Spinal synovial cysts

Extradural spinal synovial cysts originating from articular facet joint capsules that cause compression of the spinal cord have recently been described in dogs, and occur most commonly in the cervical vertebrae (Levitski et al., 1999; Dickinson et al., 2001). Further information can be found in Chapters 14 and 15.

#### Spondylosis deformans

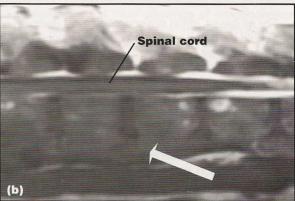
Spondylosis deformans is a degenerative, non-inflammatory, proliferative disease of the vertebral column characterized by the presence of vertebral osteophytes at intervertebral disc spaces, resulting in the formation of spurs or complete bony bridges.

Clinical signs: The condition is usually subclinical, although stiffness, restricted motion, and pain might be attributed to spondylosis deformans in a small percentage of patients. All other causes of neck pain should be ruled out before spondylosis is definitively associated with the signs.

Pathogenosis: This disease has been reported in dogs from 2 years of age, with 75% of dogs with spondylosis deformans affected to some extent by 9 years of age (Romatowsky, 1986). It has been reported with high incidence in Boxers, in which it may be an inherited condition. In this breed, it is more commonly seen in females; it can involve the whole spine, although it is more often found in the thoracolumbar spine than in the cervical spine. Trauma, degenerative disc disease and intervertebral disc fenestration have all been associated with the formation of spondylosis deformans; however, it may occur in the absence of these three. Osteophytic projections into the spinal canal causing compression of the spinal cord are rare, as is osteophytic compression. of spinal nerves at the level of the intervertebral foramina, although it has been reported at the lumbrosacral (LS) junction (see Chapter 18).

**Diagnosis:** Diagnosis is based upon ventrodorsal, lateral (Figure 13.7a) and oblique spinal radiography, but demonstrating soft tissue and neural tissue involvement requires advanced imaging such as MRI (Figure 13.7b).





Spondylosis in a 7-year-old Golden Retriever.

(a) The lateral radiograph shows marked ventral vertebral body spondylosis (arrowed); other causes of back pain should be investigated, as this osseous proliferation rarely causes neural tissue compression.

(b) The sagittal T2-weighted MR image shows spondylosis (arrowed) but with no evident cord compression.

**Treatment and prognosis:** Treatment relies on analgesia, if required, and, possibly, surgical decompression, but this is rarely needed. If spondylosis is causing clinical signs, the prognosis may be guarded, due to the high probability of recurrence and/or progression.

#### **Dural ossification**

Dural ossification is a degenerative condition of dogs of unknown aetiology, characterized by deposition of bone plaques on the inner surface of the dura mater. These plaques occur most commonly in the cervical and lumbar regions of the spine and are common incidental findings on radiographic studies of the spine; although clinical disease has been documented, due to associated spinal cord compression (Wilson *et al.*, 1975), this should primarily be regarded as an incidental finding.

#### Calcinosis circumscripta

Sometimes called tumoral calcinosis, calcinosis circumscripta (CC) has been reported to cause spinal cord compression in several breeds of dog (Bernese Mountain Dogs, German Shepherd Dogs, English Springer Spaniels, Rottweilers and Great Danes) less than a year old; compressive disease is usually localized dorsally at the atlantoaxial articulation (Lewis and Kelly, 1990). Further information is available in Chapter 14.

#### **Anomalous diseases**

#### Atlantoaxial instability

Atlantoaxial instability can lead to subluxation of the first and second cervical vertebrae; the cranial aspect of the axis often rotates dorsally with respect to the atlas, into the vertebral canal. Subsequent spinal cord

compression results in a variety of neurological signs, but may just cause cervical pain. The pathogenesis, diagnosis and treatment of this disease are discussed in Chapter 14.

#### Chiari-like malformations

Clinical signs: The condition may be acute or chronic, and can occur in dogs ranging from 6 months to 10 years of age. Clinical signs include neck pain, torticollis or scoliosis, spinal hyperaesthesia and neurological deficits relating to cervical spinal cord dysfunction. Intracranial signs, such as facial paresis and vestibular dysfunction, have also been reported. Paroxysmal involuntary scratching of the neck and flank has been associated with this condition.

Pathogenesis: Chiari-like malformations are complex developmental disorders involving the caudal brainstem, cerebellum and the cranial cervical spinal cord. The human classification of Chiari type I necessitates elongation and caudal displacement of the cerebellar tonsils (vermis and paravermal lobes) through the foramen magnum into the cranial cervical vertebral canal; the cord may be kinked, due to being pushed caudally by the brainstem. A similar condition has been documented in dogs and is apparently over-represented in Cavalier King Charles Spaniels (Rusbridge and Knowler, 2003b). A familial or genetic basis is suspected (Rusbridge and Knowler, 2003a). This condition seems to be associated with occipital bone dysplasia resulting in 'overcrowding' of the caudal fossa, obstruction of the CSF flow and secondary syringohydromyelia.

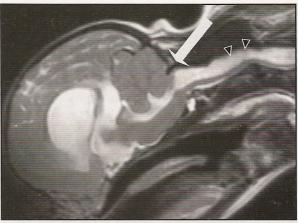
In type II malformation, there is herniation of the cerebellar vermis and sometimes portions of the lateral cerebellar hemispheres, over the dorsal aspect of the cervical spinal cord; the brainstem may also be elongated and partially located in the spinal canal, usually in association with a meningomyelocele.

*Diagnosis:* These structural abnormalities are best diagnosed with MRI (Figure 13.8), but they may be clinically silent, so their significance must be carefully considered when such abnormalities are discovered (Lu *et al.*, 2003).

Treatment and prognosis: Treatment of these conditions is either medical or surgical. Medical therapy involves the use of frusemide (2 mg/kg orally q12h) in conjunction with prednisolone (0.5 mg/kg orally q48h). Approximately 70% of patients show some improvement, but it is rarely complete (Dewey, 2003). If medical therapy does not alleviate the clinical signs, surgical decompression of the caudal fossa has been suggested (suboccipital craniectomy), and is the treatment of choice in people.

#### Perineurial (Tarlov) cysts

Perineurial cysts are rare lesions of the nerve roots that have been recently reported in two dogs (Platt *et al.*, 2003). Tarlov cysts are distinguished from other extradural meningeal lesions on the basis that:

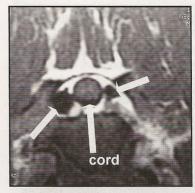


A sagittal T2-weighted cranial MR image of a 6-year-old Cavalier King Charles Spaniel. There is evident hydrocephalus and marked replacement of the spinal cord parenchyma by fluid-filled cavities (syringohydromyelia) (arrowheads). Note the caudal displacement of the vermis of the cerebellum (arrowed), associated with occipital dysplasia of the calvarium. This is compatible with a Chiari-like syndrome.

- They arise at the junction of the dorsal root ganglion and the nerve root
- They develop between the endoneurium and perineurium
- Their lining contains nerve fibres and/or ganglion cells.

In humans, excision or fenestration of these cysts is recommended, although recurrence is possible.

In the author's study, a 4-year-old spayed female Scottish Deerhound and an 8-month-old female St Bernard presented with chronic neck pain; MRI revealed fluid-filled structures at the level of vertebrae C6 and C7 (Figure 13.9). The cysts, which were attached to the nerve roots, were fenestrated. Histopathology of the capsules was compatible with perineurial cysts. On re-examination one year postoperatively, neither dog had evidence of cervical pain.



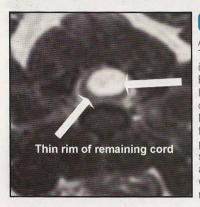
13.9

A transverse
T1-weighted MR
image of the spinal
cord of a young
Deerhound,
demonstrating fluidfilled structures
(arrowed) either side
of the spinal cord at
the level of the nerve
roots.

#### Spinal cord anomalies

These diseases include spinal dysraphism, myelodysplasia, spina bifida and syringohydromyelia. The first three usually present with neurological deficits and are described in Chapter 15. Although neurological deficits are common with syringohydromyelia, pain and persistent scratching of the neck and flank are often the first clinical signs.

Syringohydromyelia: Syringomyelia (cavitation of the spinal cord) and hydromyelia (dilation of the central canal) result in similar signs of spinal cord dysfunction. Syringomyelia may exist as a distinct entity or may exist in communication with the central canal. It is often difficult to differentiate between the two conditions and so the term syringohydromyelia is often used (Figure 13.10). The causes of this condition include congenital malformations, trauma, inflammation and neoplasia but it can also be idiopathic. Clinical signs depend on the specific spinal site of the lesion but approximately 40% have spinal pain (Dewey, 2003). This condition is discussed further in Chapter 14.



#### 13.10

A transverse T2-weighted MR image of the dog in Figure 13.8, at the level of the second cervical vertebra. Note the large fluid-filled cavity within the parenchyma of the spinal cord (right arrow) compatible with syringohydromyelia.

#### **Scoliosis**

This may be subclinical but can cause spinal discomfort (Figure 13.11). Neurological deficits may be present; these depend on the underlying cause.

Scoliosis may occur in animals with a hemivertebra. There are numerous reports of scoliosis occurring in animals with congenital or acquired cystic lesions involving the spinal cord, such as syringohydromyelia (Child *et al.*, 1986). The association has been suggested to be due to progressive destruction of grey matter by cavitation, resulting in denervation and atrophy of epaxial muscles unilaterally, followed by asymmetrical contralateral muscle spasticity and subsequent vertebral deviation.

Diagnosis of the structural cause of the scoliosis necessitates imaging studies. Treatment, if any is possible, should be directed at the underlying cause; the prognosis is guarded.



Lateral deviation of the cervical vertebrae in relation to the skull and the thoracic vertebrae, compatible with scoliosis, in a 6-month-old Cavalier King Charles Spaniel.

#### Vertebral anomalies

Many spinal anomalies do not produce any clinical signs and are detected as incidental findings; however, if a vertebral malformation is discovered in the presence of spinal pain, with or without neurological deficits, it should be thoroughly investigated. The presence of a vertebral anomaly may be a sporadic occurrence, but the potential for heritability must be considered. Many of the documented anomalies in veterinary patients occur in the thoracolumbosacral vertebrae, but they have the potential to occur anywhere in the vertebral column. They often cause signs due to associated spinal canal stenosis, progressive spinal deformity with growth or ageing, or instability exacerbated by degenerative disc disease. Important vertebral anomalies include hemivertebrae, block vertebrae, occipitoatlantoaxial malformation, hypoplasia or aplasia of the dens, transitional vertebrae and congenital spinal stenosis. These anomalies are described in Chapters 5, 14 and 15.

## **Neoplastic diseases**

Spinal cord tumours are relatively common in cats and dogs and are usually classified according to their position in relation to the spinal cord and meninges as either extradural, intradural—extramedullary or intramedullary (Figure 13.12). Intramedullary neoplasia is rarely painful. Further details on this classification and the diagnosis, treatment and prognosis of spinal tumours can be found in Chapter 15. Peripheral nerve sheath tumours are discussed in Chapter 16.

#### **Nutritional diseases**

## Hypervitaminosis A

Abnormally high levels of vitamin A have been reported in cats on predominantly liver diets. These may cause hypertrophic bone formation on the vertebrae, leading to ankylosing spondylosis, primarily of the cervical vertebrae, but in some cases this may extend to the lumbar region. Clinical signs relate to the rigidity of the spinal column and the associated pain. Treatment involves alteration of the diet, but this does not dramatically reverse the bone formation. Pain relief is recommended.

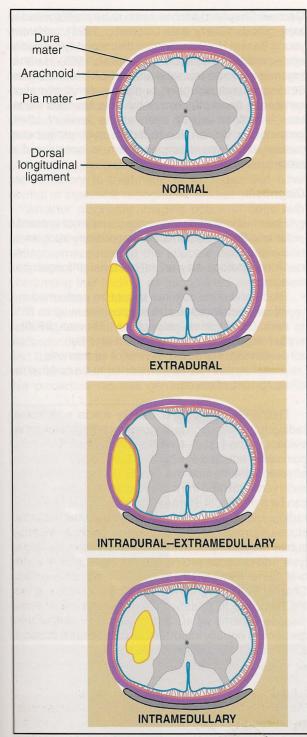
#### Inflammatory diseases

#### Infectious meningitis/meningomyelitis

Meningitis (inflammation of the meninges) and meningomyelitis (inflammation of the spinal cord and the meninges) can cause severe spinal pain. Meningomyelitis, by definition, will also cause neurological deficits. Cerebrospinal fluid (CSF) analysis is the most reliable ante-mortem diagnostic test available for identifying CNS inflammation; it often reveals an increase in the white blood cell number as well as protein elevations. A complete discussion of the diagnosis, treatment and prognosis of infectious CNS disease is presented in Chapters 10 and 15.

#### Steroid-responsive meningitis-arteritis

Clinical signs: SRMA, also termed necrotizing vasculitis, juvenile polyarteritis syndrome, corticosteroid-



The location of tumours (yellow) within the spinal canal is classified according to their location relative to the spinal cord and the dura mater.

responsive meningitis/meningomyelitis, aseptic suppurative meningitis, panarteritis and pain syndrome, is a non-infectious inflammatory condition reported in Beagles, Bernese Mountain Dogs, Boxers and German Short-Haired Pointers (Tipold and Jaggy, 1994), and probably occurs in other breeds.

Affected dogs are often young adults (8–18 months old) but may be of any age, and are usually febrile and hyperaesthetic, with cervical rigidity and anorexia (Figure 13.13). Neurological deficits can be seen in the



13.13 A 7-month-old Beagle exhibiting a stiff neck posture due to the inflammatory condition steroid-responsive meningitis—arteritis, sometimes called Beagle pain syndrome in this breed.

chronic form of this disease. Some dogs (up to 46%) with immune-mediated polyarthritis, especially Bernese Mountain Dogs, Boxers and Akitas, may show similar clinical signs to dogs with SRMA and have concurrent meningitis (Webb *et al.*, 2002). Some dogs may have concurrent glomerulonephritis.

**Pathogenesis:** An immunological cause of this disease is suspected, resulting in a vasculitis.

Diagnosis: A marked blood neutrophilia with a left shift may be seen at the time of the clinical signs. Cerebrospinal fluid often reveals a marked neutrophilic pleocytosis and protein elevation; cell counts of >100 cells/μl are common. Neutrophils are non-degenerative, unlike bacterial meningitis. In the majority of dogs with either acute or chronic disease, there are elevations of IgA levels in the CSF and the serum, although this is not specific for this disease.

Treatment and prognosis: The prognosis can be good if dogs are treated early and aggressively with immunosuppressive doses of corticosteroids (Figure 13.14). Infectious diseases should be ruled out before this treatment is initiated. The treatment is long term, and has been reported to be required for over 2 years in some dogs; however, after this time, serum and CSF IgA

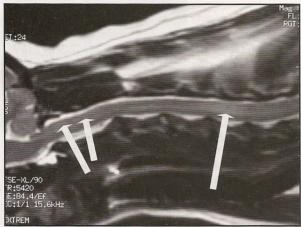
- 1. Prednisolone 4 mg/kg q24h orally or i.v. for 2 days
- 2. Prednisolone 2 mg/kg q24h orally for 14 days. If clinical signs have improved, a further reduction can be considered
- 3. Prednisolone 1 mg/kg q24h orally for 28 days. If clinical signs are normal, a further reduction can be considered
- Prednisolone 0.5 mg/kg q24h orally for 28 days. If clinical signs are normal, a further reduction can be considered
- 5. Prednisolone 0.5 mg/kg q48h orally for 2 months. If clinical signs are normal, the medication can be stopped
- 6. Azathioprine 2 mg/kg q24h reducing to 1.5 mg/kg every other day orally if clinical signs are refractory to the steroid medication

13.14 Treatment recommendations for steroid-responsive meningitis—arteritis.

levels were still elevated in some dogs (Cizinauskas *et al.*, 2000). Monitoring of CSF cell count in dogs with this condition is a sensitive indicator of success of treatment.

Granulomatous meningoencephalomyelitis

Granulomatous meningoencephalomyelitis (GME) is a non-suppurative CNS inflammatory disease of undetermined aetiology in dogs. It is suggested to be a T-cell-mediated delayed-type hypersensitivity (Kipar *et al.*, 1998). It is most commonly seen in small-breed dogs, and often in terriers, toy breeds and Poodles, although any breed may be affected (Muñana and Luttgen, 1998). GME may involve the spinal cord at any level; however, lesions appear to be most severe in the cervical spinal cord (Figure 13.15). Findings include apparent cervical pain, rigidity, reluctance to move, hyperaesthesia, cervical paraspinal muscle spasms and neurological deficits. Further information on the pathophysiology, diagnosis and prognosis of this disease is contained in Chapter 10.



A T2-weighted sagittal MR image of the cervical spinal cord of an 8-year-old West Highland White Terrier with severe neck pain due to granulomatous meningoencephalomyelitis. Note the multifocal hyperintense inflammatory lesions within the cord (arrowed). This is not specific for this disease; CSF analysis is always necessary to document the inflammatory nature of the condition.

## Discospondylitis/osteomyelitis

Clinical signs: Spinal pain is the most common initial clinical sign in this disease, which is most frequently seen in large intact male middle-aged dogs. Although it can occur in any animal, the condition is less common in toy and chondrodystrophoid breeds of dog, as well as in cats. Approximately 30% of dogs have signs of systemic illness such as fever and weight loss.

Pathogenesis: Discospondylitis is due to infection of the intervertebral disc and adjacent vertebrae; if the infection is confined to the vertebral body, it is called vertebral osteomyelitis or spondylitis (Thomas, 2000). Staphylococcus intermedius is the most common aetiological agent of canine discospondylitis; other less commonly identified organisms include Streptococcus spp., Escherichia coli, Actinomyces spp. and Brucella canis, as well as Aspergillus spp. Young

German Shepherd bitches seem to be predisposed to aspergillosis (Berry and Leisewitz, 1996), whereas young Basset Hounds contract discospondylitis due to systemic tuberculosis (Carpenter *et al.*, 1988). Haematogenous spread from distant foci of infection, penetrating wounds, surgery, or plant material migration can cause direct infection of the disc space or vertebrae, which is usually seen at the level of L2–4. Immunosuppression due to factors such as diabetes mellitus and hyperadrenocorticism is considered a predisposing cause.

## Diagnosis:

- Haematological changes are usually not present unless there are concurrent conditions such as endocarditis
- Urine cytology may reveal bacterial or fungal agents
- Blood and urine cultures should be performed in all suspected cases and are positive in up to 75% and 50% of cases, respectively (Thomas, 2000)
- Serology for brucellosis should also be performed, especially in view of its zoonotic potential; this has been reported to be positive in up to 10% of cases.

Definitive diagnosis is usually made with spinal radiographs, although radiographic change may not be evident in the first 2-4 weeks of infection. The most commonly affected site is L7-S1, but other frequently affected sites include the caudal cervical/cranial thoracic vertebrae and the thoracolumbar junction. As this can be a multifocal disease, the entire spine should be radiographed. Radiographic evidence of disease includes narrowing of the disc space, accompanied by subtle irregularity of both endplates through to gross lysis and osseous proliferation of the adjacent vertebral bone (Figure 13.16) and even fractures (see Chapter 5). Radiography can also be used to monitor the response to treatment or the progression of the disease (Shamir et al., 2001), although clinical progression is equally important, as radiographic change can lag behind clinical improvement. Myelography is indicated in patients with substantial neurological deficits to rule out concurrent disc disease; however,



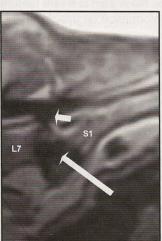
A lateral radiograph of an 8-year-old Airedale with lumbar pain. Gross irregular lysis and osseous proliferation of the vertebral endplates of L7 and S1 (arrowed) can be seen, compatible with discospondylitis.

this should be reserved for the cases that are refractory to antibiotic therapy, when a surgical treatment may be considered.

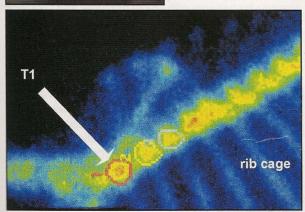
Computed tomography (CT) can identify subtle endplate erosion and paravertebral soft tissue swelling more readily than radiography. Post-myelogram CT clearly defines compression of the neural tissues by infected tissues, as does MRI (Figure 13.17). MRI can also highlight the inflammation in the surrounding muscles. However, as radiographs can be diagnostic, advanced imaging studies are reserved for cases that are refractory to treatment, or for those that have normal or equivocal radiographic studies.

Another diagnostic imaging option in dogs with discospondylitis is technetium-99m bone scanning (scintigraphy), which shows an increased uptake of the radiopharmaceutical at the affected disc space and endplates (Figure 13.18). Care must be taken when interpreting this finding, as spondylosis also causes some increase in uptake.

If urine and blood culture, and brucellosis serology, have not identified an aetiological agent in cases of discospondylitis, percutaneous needle aspiration of the disc space can be a safe procedure to obtain tissue for bacterial and fungal cultures and cytology. However, this procedure requires general anaesthesia, sterile



A sagittal 13.17 T2-weighted MR image of the same region of the dog shown in Figure 13.16. The bony detail is not as good as with radiography. A loss of signal is seen in the region of the osseous proliferation (long arrow) which is not specific for vertebral infection. However, in cases unresponsive to antibiotic therapy MRI may help identify associated neural compression (short arrow).



Scintigraphy can be performed to investigate for vertebral lesions, as demonstrated in this lateral view of the cervicothoracic spine of a 10-year-old Ibizan Hound. The accumulation of the radioisotope within the body of the first thoracic vertebra (arrowed) is not specific for discospondylitis though, and vertebral body tumours can look similar.

surgical preparation and fluoroscopic or CT guidance of the needle, and is usually only performed in patients unresponsive to initial broad-spectrum antibiotics. The procedure has been documented to be up to 75% sensitive (Fischer et al., 1997); open biopsy of the vertebrae may be considered if needle aspiration is unrewarding. This has yielded positive cultures in approximately 80% of patients (Kornegay and Barber, 1980).

In all cases, diagnostic investigation of potential systemic infectious foci should be considered. This should include abdominal ultrasonography for prostatic or renal disease, thoracic radiographs for pulmonary disease, and cardiac ultrasonography for endocardial disease.

Treatment and prognosis: Once radiographic evidence of discospondylitis is present, treatment for the common potential pathogen Staphylococcus intermedius may be started. The treatment of discospondylitis consists of antibiotics, cage rest and analgesics (Figure 13.19). Results of cultures may require alteration of this choice.

Infectious agent	Antibiotic	Dosage
Staphylococcus intermedius	Cefalexin Cefazolin Amoxicillin	20–30 mg/kg orally q8h 20 mg/kg i.v., i.m. or s.c. q6h 20 mg/kg orally q12h
Beta-haemolytic Streptococcus spp.	Amoxicillin	20 mg/kg orally q12h
Escherichia coli	Enrofloxacin	5-11 mg/kg orally q12h
Brucella canis	Enrofloxacin Doxycycline	10–20 mg/kg orally q24h 25 mg/kg orally q24h
Aspergillus spp.	Fluconazole	2.5-5 mg/kg orally q24h

13.19

Drug therapy for discospondylitis/osteomyelitis.

Intravenous antibiotics should be considered if severe neurological compromise is present; otherwise, oral antibiotics are acceptable. However quickly the patient improves, continuation of the antibiotics for 8 weeks is recommended (Thomas, 2000). Resolution of clinical signs, such as pain and fever, should be expected within 5 days of initiating therapy; however, complete neurological resolution may take 2-3 months. Residual deficits may remain, but persistent pain indicates an active disease, and these patients should be treated with an additional antibiotic and considered for further diagnostics as they may have a potential fungal infection or surgical lesion.

Surgical decompression is rarely needed, and should only be considered in refractory cases or those with severe neurological deficits that show no sign of improvement within 3-5 days.

Non-steroidal anti-inflammatory drugs should be considered in dogs for the treatment of pain while awaiting the effect of the antibiotics, but should not be necessary after 5 days and should be discontinued to allow clinical assessment of the patient. Corticosteroids are not appropriate anti-inflammatories in this disease.

The prognosis for this disease is generally very good unless the aetiology is fungal or there is endocarditis; the potential for recurrence should be considered, especially if brucellosis has been diagnosed or an underlying immunosuppressive condition is present. Residual neurological deficits are possible, and in those cases that have severe neurological deficits associated with the infection the prognosis should initially be guarded.

#### **Empyema**

Infection of the CNS may result in an abscess or empyema in subdural or epidural locations. Epidural infections can follow skin disease, vertebral osteomyelitis, discospondylitis or a paraspinal abscess. Clinical signs may include fever, anorexia, lethargy and apparent spinal pain, as well as neurological compromise; however, there may not be a systemic reaction. Further information on this condition is found in Chapter 15.

#### Polymyositis/polymyopathies

The main sign of a disease affecting the skeletal muscles is weakness; however, muscle pain (myalgia) may also be a feature, which may present as spinal pain. The weakness accompanying the muscle disease may be discrete, causing an abnormal posture such as neck ventroflexion, especially in cats, leading the clinician to focus on a cervical disease. For a complete discussion of muscle disease, the reader is directed to Chapter 17.

### **Polyarthritis**

Arthritis is generally classified as either non-inflammatory or inflammatory (Figure 13.20). Inflammatory

#### Non-inflammatory

Degenerative joint disease

#### Inflammatory

#### Infectious (septic)

## Immune-mediated (non-septic):

Erosive

Canine rheumatoid arthritis

Feline progressive polyarthritis

Periosteal proliferative polyarthritis

Polyarthritis of Greyhound

### Non-erosive

Systemic lupus erythematosus

Polyarteritis nodosa

Polyarthritis/meningitis

Lymphocytic-plasmacytic synovitis

Amyloidosis of Shar-Pei

#### Idiopathic:

- Type I (uncomplicated)
- Type II (reactive)
- Type III (enteropathic)
- Type IV (malignant)

#### Vaccine 'reactions'

#### Drug-induced

13.20 Classification of arthritis.

joint diseases can affect multiple joints (polyarthritis) and are either infectious or immune-mediated. Immune-mediated polyarthritides can be further classified as erosive or non-erosive, based on the presence or absence of joint cartilage destruction and typical bone erosion visible on radiographs. Polyarthritis can often present as a spinal pain syndrome, but there is commonly appendicular joint pain present as well. Typically, animals appear to be 'walking on eggshells', and are reluctant to lie down or to rise once down. All appendicular joints should be carefully palpated but the absence of a joint effusion does not rule out polyarthritis. The prevalence of spinal pain in dogs with non-infectious non-erosive idiopathic immunemediated polyarthritis is approximately 30% (Webb et al., 2002). The reader is directed to internal medicine and orthopaedic texts for a more complete discussion on the diagnosis and management of these conditions.

## Idiopathic diseases

## Arachnoid cysts

Also termed subarachnoid cysts, meningeal cysts, intra-arachnoid cysts, leptomeningeal cysts and arachnoid diverticula; these developmental abnormalities have been documented in dogs (Rylander *et al.*, 2002) and, less commonly, cats. Neck pain is a rare feature of this disease. Further information on this disease is provided in Chapter 14.

## Traumatic diseases

## Spinal fracture or luxation

Vehicle-related injury is the most common exogenous cause of trauma to the spine in small animals; however, falls, trauma from falling objects, and kicks from farm animals and horses are also possible. Depending on the type of force, the area of impact and the inherent strengths and weaknesses of the vertebral column, exogenous spinal injury often results in vertebral fracture, subluxation or luxation. Cervical and thoracolumbar vertebral injuries are discussed in detail in Chapters 14 and 15, respectively. The medical considerations for patients with spinal fractures and luxations are discussed in Chapter 19.

## Vascular diseases

#### Spinal haemorrhages

Intramedullary, intrameningeal or epidural haemorrhage may be due to coagulopathies, or associated with tumours, vascular malformations, acute intervertebral disc protrusion, trauma, parasitic migration or meningitis. Neurological deficits depend on the location of the haemorrhage and usually indicate an acute focal or multifocal myelopathy accompanied by severe pain. A more detailed description of these diseases is contained in Chapter 14.

## References and further reading

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# **Tetraparesis**

# Natasha J. Olby

## Introduction

- Tetraparesis is defined as reduced voluntary motor function in all four limbs, and can be subdivided into ambulatory and nonambulatory categories.
- Tetraplegia indicates total absence of voluntary motor function in all four limbs.

Tetraparesis can result from focal diseases of the brainstem and spinal cord, or generalized diseases of the peripheral nervous system (PNS), including diseases of the neuromuscular junction and muscle. It can also be caused by non-neurological diseases (Figure 14.1). A careful physical and neurological examination is therefore needed to localize the source of weakness.

Polymyositis (see Chapter 17) Polyarthritis Hypertrophic osteodystrophy Hypoglycaemia Hypoxaemia Hypotension

14.1

Non-neurological diseases that can cause tetraparesis.

This chapter discusses how to approach a tetraparetic animal and describes the features, treatment and prognosis of the more commonly encountered diseases. Managemental issues specific to the recumbent animal are discussed further in Chapter 24. Surgery is the recommended treatment for many spinal diseases; basic approaches to the spine, and the indications for and complications of spinal surgery, are discussed further in Chapter 21. Surgical texts for additional specific details include Wheeler and Sharp (1994) and Slatter (2002).

# **Clinical signs**

In tetraparetic animals the pelvic limbs are often affected earlier and more severely than the thoracic limbs, and severity of signs can range from mild weakness and ataxia to tetraplegia with respiratory failure.

Tetraplegic animals are at serious risk of respiratory failure due to paresis of the intercostal muscles and diaphragm, atelectasis as a result of recumbency, aspiration pneumonia, or failure of respiratory drive (if the brainstem is involved).

Animals with central nervous system (CNS) causes of tetraparesis are ataxic and have conscious proprioceptive and postural reaction deficits in all four limbs. Neck pain may be present, depending on the aetiology of signs and the individual (see Chapter 13). Myotatic reflexes and muscle tone in the pelvic limbs are normal to increased; in the thoracic limbs they may be normal to increased, or decreased, depending on the neurolocalization (C1-5 and C6-T2, respectively). Caudal cervical lesions can cause: lameness in one or both thoracic limbs; a short, stilted thoracic limb gait; muscle atrophy of the supra- and infraspinatous and biceps brachii muscles; and at rest animals may hold the affected limb(s) off the ground. These signs are a result of compression of nerve roots causing pain and weakness (nerve root signature). Lateralized cervical spinal cord lesions can produce partial Horner's syndrome (miosis) on the affected side as a result of involvement of the sympathetic fibres running in the lateral funiculus of the spinal cord and emerging from the spinal cord at segments T1-3. Lesions affecting spinal cord segments C8-T2 can affect the motor (effector) arm of the cutaneous trunci reflex, the lateral thoracic nerve, causing complete loss of the reflex on the affected side. In addition to tetraparesis, brainstem involvement causes cranial nerve deficits, in particular vestibular dysfunction, and can cause changes in mentation. In both brainstem and spinal cord disease, lateralized lesions produce ipsilateral deficits (e.g. hemiparesis).

Generalized lower motor neuron (LMN) diseases cause weakness characterized by decreased muscle tone (flaccidity) and decreased or absent myotatic reflexes. Ataxia and postural reaction and conscious proprioceptive deficits may also be present. Involvement of the recurrent laryngeal nerve can cause a change in, or loss of, voice (dysphonia) and increased inspiratory noise (stridor). The development of megaoesophagus can cause regurgitation, often with accompanying aspiration pneumonia, particularly if the pharyngeal and laryngeal muscles are concurrently involved. Other cranial nerve deficits such as facial paresis may be present. As disease progresses, dramatic muscle atrophy develops; although muscle hypertrophy occurs in some

myopathies and peripheral neuropathies. Myopathies can usually be distinguished from neuropathies as myotatic reflexes are usually normal and there are no conscious proprioceptive deficits. However, adequate support must be given to very weak animals in order to test conscious proprioception accurately. Exercise intolerance can be the only sign present in some myopathies and disorders of neuromuscular transmission, such as myasthenia gravis. (See Chapter 17 for further details of these diseases.)

Any animal that is tetraplegic, whether the cause is spinal or peripheral in origin, is at risk from hypoventilation and so an arterial blood gas analysis should be performed to measure the partial pressure of carbon dioxide. Ventilatory support by means of a mechanical ventilator may be necessary in animals with an arterial partial pressure of CO2 of >50-60 mmHg. In small animals (<5 kg) a transtracheal catheter can be used in place of a ventilator. The catheter is advanced via the cricothyroid ligament to the level of the bronchial bifurcation, and a humidified oxygen/ air mixture is passed through the catheter at a rate sufficient to exchange carbon dioxide adequately. Any animal with regurgitation is at risk of developing aspiration pneumonia: the lung fields should be auscultated carefully, and thoracic radiographs and an

arterial blood gas analysis performed if there is any suspicion of aspiration.

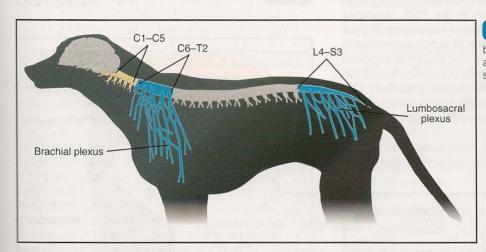
Non-neurological causes of tetraparesis should be suspected whenever conscious proprioception is normal. Careful palpation of joints and long bones will enable the clinician to identify orthopaedic diseases such as polyarthritis and hypertrophic osteodystrophy.

## **Lesion localization**

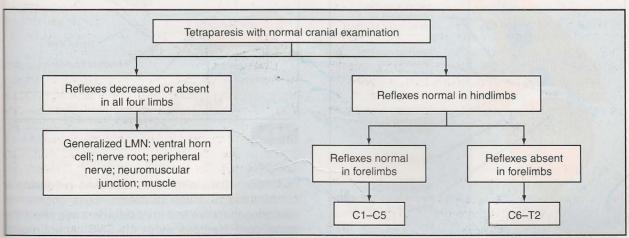
Tetraparesis can result from:

- Focal lesions in the cervical spinal cord or brainstem
- · Diffuse spinal cord diseases
- Generalized diseases of the peripheral nerve, neuromuscular junction and muscle.

Figure 14.2 illustrates the parts of the nervous system affected; details of neurological examination and lesion localization are covered in Chapters 1 and 2. Once the neurological examination has been completed, Figure 14.3 can be used to differentiate spinal cord disease from generalized LMN disease. Brainstem disease is considered in Chapter 10.



Lesion localization for tetraparesis; the brainstem, cervical spinal cord and peripheral nervous system are highlighted.



An approach to localizing the neurological signs in tetraparetic animals with a normal cranial nerve examination and mentation. LMN = lower motor neuron.

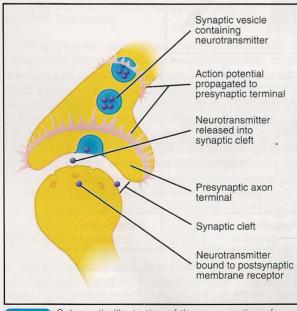
## **Pathophysiology**

Conduction of nerve impulses is dependent on the integrity of the neuronal cell body, the axon, the myelin sheath and the junction between a neuron and its target. Neurons have excitable membranes due to selective ionic permeability. In the resting state, the membrane is polarized to a potential of approximately -70mV as a result of partial permeability to potassium and active extrusion of sodium in exchange for potassium.

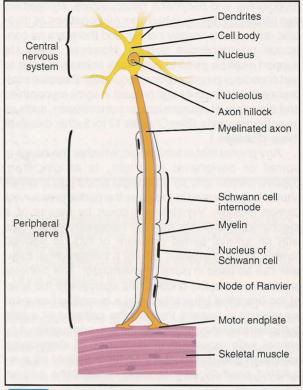
Action potentials are generated by rapid influx of sodium through voltage-dependent channels that are opened by depolarization of the membrane. This membrane depolarization results from the activation of receptors by neurotransmitters: either excitatory (causing membrane depolarization) or inhibitory (causing membrane hyperpolarization) (Figure 14.4). The membrane is repolarized by closure of the sodium channels (halting the influx of sodium) and opening of voltage-dependent potassium channels (producing efflux of potassium). Action potentials that conduct down the axon are triggered at the axon hillock (the junction between the axon and neuronal cell body; Figure 14.5).

Speed of conduction is largely dependent on axon diameter (larger diameter conducts more quickly) and myelination. Myelin, produced by oligodendrocytes in the CNS and Schwann cells in the PNS, insulates axons, increasing their membrane resistance (Figure 14.6). This causes conduction of action potentials in a simple cable fashion to the next region of exposed axon membrane (node), where depolarization of the membrane produces a new action potential. The result is conduction of the impulse from node to node in a saltatory fashion, dramatically increasing the speed of conduction.

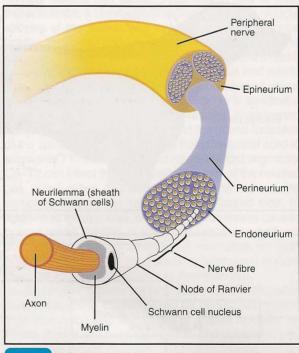
Spinal cord dysfunction most commonly results from compression, concussion, laceration, ischaemia



Schematic illustration of the propagation of a neuronal axon potential.



14.5 The structure of a somatic neuron.



14.6 The structure of a peripheral nerve.

or inflammation, with many diseases producing a combination of these problems. Less commonly, neurodegenerative and toxic disorders can affect the spinal cord. Neurons within the CNS cannot regenerate axons and so recovery following axonal transection or neuronal death depends on the development

of alternative routes of conduction using surviving tissue. As a result, prognosis in spinal cord disease, no matter what the aetiology, is greatly influenced by the severity of damage at the time of evaluation.

Treatment of spinal cord diseases focuses on surgical decompression of compressive lesions, appropriate treatment of infectious and inflammatory diseases and physical therapy to facilitate and maximize recovery.

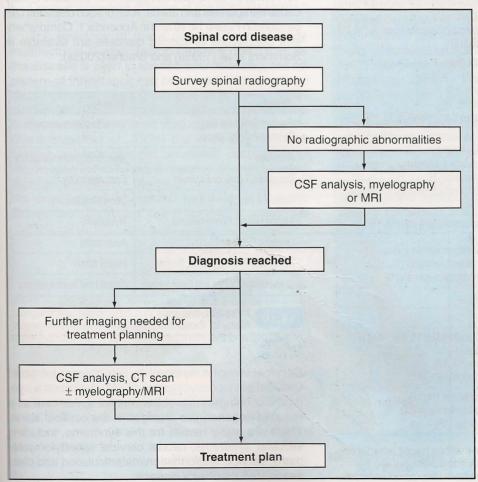
Neurons in the PNS are more resistant to injury than their CNS counterparts and are able to regenerate axons at a surprising speed (1–4 mm/day) if they are regenerating within an intact endoneural and Schwann cell tube. However, when a nerve is completely severed and displaced (neurotmesis), successful regeneration to a target only occurs if the axon is able to find the distal stump of the nerve.

Although the same basic injury types apply to peripheral nerves, metabolic, inherited and toxic disorders assume a greater clinical importance than in the spinal cord. In most peripheral neuropathies a mixture of demyelination and axonal degeneration is present. The distal ends of axons are particularly susceptible to degeneration as a result of their distance from the neuronal cell body, with longer nerves (recurrent laryngeal and sciatic nerves) often clinically affected first in toxic, degenerative and metabolic disorders.

# **Neurodiagnostic investigation**

The history and findings of the physical and neurological examinations will allow identification of a neurological problem and localization to brainstem, spinal cord or PNS. Diagnostic evaluation of animals with evidence of spinal cord disease starts with routine blood work (complete blood cell count, serum biochemical analysis and urinalysis) and survey spinal radiographs. Survey thoracic radiographs should be taken in any animal in which neoplasia is a differential, to identify metastatic disease. Decisions based on findings from spinal radiographs can be made using the flow chart in Figure 14.7. As a general rule, if a diagnosis cannot be reached from survey radiographs, the animal should be referred to a specialist centre for further evaluation, including advanced imaging.

Minimum diagnostic work-up for dogs with generalized LMN signs includes a complete blood cell count, serum biochemical panel including creatine kinase (CK), urinalysis, and chest radiographs to identify megaoesophagus, aspiration pneumonia and pulmonary metastases. Figure 14.8 illustrates the diagnostic approach used to evaluate these cases further. Although nerve and muscle biopsies may provide a definitive diagnosis, further testing is often needed based on biopsy results (see below for diagnostic tests for specific diseases and Chapter 6 for biopsy techniques).

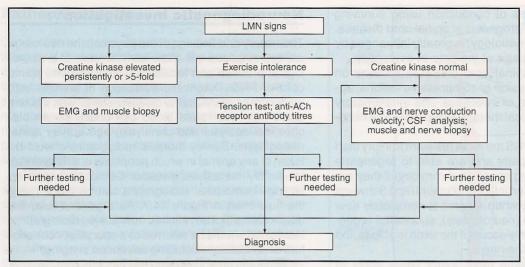


In animals with spinal cord disease, the need for further diagnostic testing depends on the results of survey spinal radiography.

CSF = cerebrospinal fluid;

CT = computed tomography;

MRI = magnetic resonance imaging.



Animals 14.8 with lower motor neuron (LMN) signs often need an electrophysiological evaluation, coupled with biopsy of nerve or muscle, to determine the most appropriate treatment. ACh = acetylcholine; CSF = cerebrospinal fluid; EMG = electromyography.

## **Spinal cord diseases**

Spinal cord diseases that can cause tetraparesis are listed in Figure 14.9.

Mechanism of disease	Specific diseases	
Degenerative	Inherited neurodegenerative diseases (Figure 14.10) [14] Calcinosis circumscripta [14] Cervical stenotic myelopathy (Wobbler syndrome) [14] Degenerative myelopathy [15] Intervertebral disc disease (Hansen type I and II) [14, 15] Spinal synovial cysts [14]	
Anomalous	Atlantoaxial instability [14] Dermoid sinus [14, 15] Osteochondromatosis [15] Syringohydromyelia [13, 14] Vertebral and spinal cord anomalies [5, 13, 15]	
Neoplastic	Extradural: metastasis; vertebral tumours (sarcomas, plasma cell tumours); lymphoma [15] Intradural–extramedullary: meningiomas; nerve sheath tumours; metastasis [15] Intramedullary: ependymomas; gliomas; metastasis; round cell tumours [15]	
Inflammatory	Discospondylitis/osteomyelitis/physitis [13, 15] Empyema [14] Granulomatous meningoencephalomyelitis [10] Infectious meningoencephalomyelitis [10, 15] Steroid-responsive meningitis—arteritis [13]	
Idiopathic	Arachnoid cysts [14]	
Toxic	Tetanus [14]	
Trauma	Vertebral fractures/luxations [14, 15, 19] Epidural haemorrhage [14] Spinal cord contusion [14, 19] Traumatic disc herniation [14]	
Vascular	Fibrocartilaginous embolism [14, 15] Spinal cord/epidural haemorrhage [14] Thromboembolic disease [15]	

Spinal cord diseases that can cause tetraparesis.
The numbers in square brackets denote the
Chapters in which the conditions are discussed in detail.

## Degenerative diseases

#### Breed-specific spinal cord disease

These are degenerative CNS diseases that are often inherited. They cause progressive signs and usually involve many areas of the CNS. The most common neurodegenerative disease specific to the spinal cord is degenerative myelopathy of German Shepherd Dogs and Pembroke Welsh Corgis (with sporadic reports in other breeds). As the predominant signs of this disease are paraparesis and ataxia, it will be discussed in Chapter 15. However, some neurodegenerative diseases initially cause tetraparesis and ataxia. A list of such diseases can be found in Figure 14.10 and in Appendix 1. Comprehensive discussions of specific diseases are available in Summers *et al.* (1995a) and Braund (2003a).

Breed	Disease
German Shepherd Dog, Pembroke Corgi, others	Degenerative myelopathy
Rottweiler	Leucoencephalomyelopathy
Dalmatian, Labrador Retriever	Leucodystrophy
Miniature Poodle	Demyelination
Afghan Hound, Kooiker Hound	Myelopathy
Labrador Retriever	Axonopathy
Fox Hound, Harrier Hound, Beagle	Hound ataxia
West Highland White and Cairn terriers	Globoid cell leucodystrophy

14.10 Inherited diseases that can cause UMN signs. Many of these diseases also affect other areas of the CNS and therefore cause other (e.g. cerebellar) signs.

# Cervical stenotic myelopathy (Wobbler syndrome)

Cervical stenotic myelopathy (CSM) describes a syndrome of compression of the cervical spinal cord as a result of degenerative changes in the cervical spine. There are many names for this syndrome, including Wobbler syndrome, caudal cervical spondylomyelopathy, cervical malformation/malarticulation and discassociated Wobbler's disease.

Clinical signs: Classically this is thought of as a disease of large dog breeds (e.g. Dobermann Pinscher, Dalmatian) and giant breeds (e.g. Great Dane, English Mastiff) but identical changes occur in toy and small breeds such as Chihuahua and Yorkshire Terrier.

Clinical signs include progressive ataxia, tetraparesis and, sometimes, neck pain. Signs in the pelvic limbs are more severe than the thoracic limbs. Dogs with caudal cervical compression frequently have a short stilted thoracic limb gait with a dysmetric, disconnected pelvic limb gait. Nerve-root entrapment can cause thoracic limb lameness and muscle atrophy; in particular, compression of the suprascapular nerve can produce marked atrophy of the supra- and infraspinatous muscles, making the scapula spine easily palpable. Although typically this is a chronic progressive disease, acute onset of severe signs can occur.

**Pathogenesis:** Progressive spinal cord compression results from degenerative changes in the vertebral column (Trotter *et al.*, 1976). The changes (Figure 14.11) include any of the following:

- Hypertrophy and protrusion of the annulus fibrosus, often associated with 'tipping' of vertebrae
- Hypertrophy of the ligamentum flavum and dorsal longitudinal ligament
- Hypertrophy of synovial membrane and formation of synovial cysts at the articular facets
- · Stenosis of the vertebral canal
- Degenerative joint disease of the articular facets.

The aetiology of these changes is most likely multifactorial. Genetic factors probably play a role, as the disease is seen in specific breeds of dog, but no pattern of inheritance has been established in commonly affected breeds (Burbridge *et al.*, 1994). Overnutrition and excess calcium supplementation in the first year of life have been implicated in Great Danes (Hedhammer *et al.*, 1974) but correction of these feeding patterns has not prevented occurrence of the disease in this breed. It has also been postulated that conformation of the head and neck influences the development of lesions; however, a study on Dobermann Pinschers failed to find a correlation

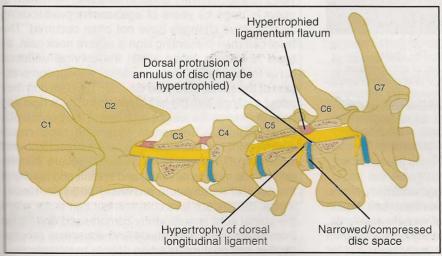
between various body dimensions and radiographic or neurological signs (Burbridge *et al.*, 1994). It is believed by many that the degenerative changes seen in this syndrome ultimately result from instability in the cervical spine.

In general, giant breeds present within the first 3 years of life with degenerative changes of the articular facets and their associated synovium, synovial cysts and stenosis of the vertebral canal affecting C3-C6. Large breeds are more likely to present with what has been termed disc-associated Wobbler's disease or caudal cervical spondylomyelopathy. They develop signs in middle age or older as a result of hypertrophy and protrusion of the annulus, and ligamentous hypertrophy of the dorsal longitudinal ligament and the ligamentum flavum, affecting the caudal cervical vertebrae. The changes in large breeds can be described as static (spinal cord compression not altered by flexion, extension or traction) or dynamic (compression altered by flexion, extension or traction). In both large and giant breeds, compressive lesions may be present at more than one site.

Diagnosis: Survey radiographs of the cervical spine may show degenerative changes typical of this syndrome (Figure 14.12) but cannot be used to identify sites of spinal cord compression. Stressed views should not be taken as compression of the spinal cord can be exacerbated. Myelography combined with computerized tomography (CT) can be used to diagnose CSM and to plan surgery (Figure 14.13). Linear traction views of the myelogram are used to determine whether compression can be addressed by distraction and fusion of vertebrae (i.e. a dynamic lesion) (Sharp et al., 1992). Magnetic resonance imaging (MRI) is being increasingly used to identify sites of compression, particularly in giant breeds (Lipsitz et al., 2001).

#### Treatment and prognosis:

Conservative management: It is recommended that dogs with neurological deficits are treated surgically, as this is a chronic progressive disease. However, many owners cannot afford or do not wish to have surgery performed and conservative therapy can be



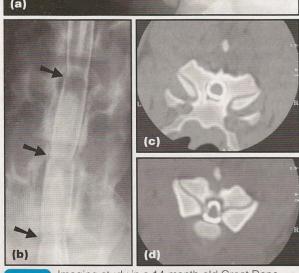
Abnormalities that may contribute to cervical stenotic myelopathy in the caudal cervical spine are shown at C5–C6. The normal relationship of the soft tissues is shown at C2–C3 and C3–C4.





Lateral cervical radiograph (a) and myelogram (b) from an 8-year-old Dobermann Pinscher with cervical stenotic myelopathy. Note the tipping of C6. The myelogram reveals severe compression of the spinal cord at C5–C6 and C6–C7.





Imaging study in a 14-month-old Great Dane with ataxia and tetraparesis. The lateral myelogram (a) does not reveal any sites of compression, but the VD view (b) shows three sites of lateral compression of the caudal cervical spinal cord (arrowed). (c) Transverse CT myelogram at the centre of the vertebral body at C5, showing the normal appearance of the spinal cord. (d) Transverse CT myelogram at the level of the articular processes, highlighting the lateral compression of the spinal cord by the enlarged processes.

considered in such cases and in dogs with mild deficits. Conservative management includes treatment of pain with anti-inflammatory drugs and muscle relaxants, and restriction of unmonitored activity combined with controlled exercise and physical therapy (see Chapter

24). Acupuncture can be useful for controlling chronic pain in some dogs. Dogs managed in this way should be monitored weekly to biweekly to allow early recognition of deterioration and recommendation for surgical intervention. Dogs that are non-ambulatory may respond to conservative management but surgery is strongly recommended.

Surgical management: The aims of surgery are to decompress and/or stabilize the cervical spine. Surgical strategies include the ventral slot (to remove disc material from the canal), distraction/stabilization techniques (to treat lesions responsive to traction) and dorsal laminectomy (to remove dorsal compression or address multiple disc protrusions). Surgical decisions are based on the type and number of lesions present and a full discussion of the different surgeries can be found in McKee and Sharp (2002). Postoperative rehabilitation of patients is critical to their recovery and owners need to be fully informed about the implications of rehabilitating a non-ambulatory large or giant breed dog (see Chapter 24). Rehabilitation includes passive range-of-motion exercises and massage in the recumbent dog, and hydrotherapy and controlled exercise if the animal is ambulatory. Due to the chronic nature of the disease, recovery of these dogs can be prolonged (6-12 weeks or more).

When dogs with disc-associated Wobbler's disease are considered, success rates with surgery are about 80% in the short term (< 1 year) (Jeffery and McKee, 2001). The presence of multiple lesions and severe neurological deficits (i.e. non-ambulatory) worsens the prognosis. The prognosis in the long term is not as good, with a recurrence of signs developing in about 20% of dogs. This is usually a result of new lesions developing at sites adjacent to the previous surgery (the domino effect) (Rusbridge *et al.*, 1998) Early surgical fusion of suspicious sites adjacent to the main lesion may help to reduce this problem in the future.

#### Cervical disc disease

Clinical signs: Onset of signs can occur from 18 months of age, with a peak incidence between 3 and 7 years of age. It is very unusual for a disc herniation to occur in dogs <2 years of age, as the predisposing degenerative changes have not often occurred. The most common presenting sign is severe neck pain, as there is enough space within the cervical vertebral canal for herniation of disc material without compression of the spinal cord (see Chapter 13). The dog may adopt a stance with the head held down, neck rigid and back arched as the weight is shifted to the pelvic limbs (see Chapter 13). Entrapment of nerve roots can cause a nerve-root signature (holding up a thoracic limb and lameness). The neck pain can be so severe that the dog avoids moving its head, and spasm and rigidity of the cervical musculature are easily palpable. Neurological deficits are less common but can occur when the spinal cord is sufficiently compressed and range from tetraparesis with ataxia and conscious proprioceptive and postural-reaction deficits to tetraplegia.

Pathogenesis: Cervical disc disease is a common problem in chondrodystrophoid breeds of dog such as Dachshund, Shih Tzu and Pekingese, It also occurs frequently in Beagles and Cocker Spaniels and can occur sporadically in almost any breed. Thoracolumbar disc herniations are well recognized in cats (see Chapter 15); cervical disc herniations have been reported (Lu et al., 2002) but are extremely rare in this species. The intervertebral disc is composed of an outer fibrous portion (the annulus fibrosus) and a gelatinous centre (the nucleus pulposus). With normal ageing the nucleus is slowly replaced by fibrocartilage (fibroid metamorphosis), but in chondrodystrophoid breeds the nucleus ages prematurely and the nucleus matrix degenerates and mineralizes (chondroid metamorphosis) (Bray and Burbridge, 1998a,b). As a result of these degenerative changes, affected dogs are prone to extrusion of the mineralized nucleus pulposus into the spinal canal (Hansen type I disc herniations), causing spinal cord concussion and compression (Figure 14.14). The C2/3 disc is most commonly affected, with incidence decreasing further caudally in the cervical spine (Dallman et al., 1992).

Vertebra Spinal cord Dorsal longitudinal Annulus fibrosus (fibrous laminae) Nucleus pulposus NORMAL Cord compression resulting from nucleus within the spinal canal Nuclear extrusion (Hansen type I disc disease) Nucleus undergoes chondroid metamorphosis with invasion by hyaline cartilage **EXTRUSION** Annular protrusion (Hansen type II disc disease) resulting from fibroid metamorphosis **PROTRUSION** 

Schematic overview of the normal structure and anatomical relationship of the intervertebral disc and the pathological changes seen with disc extrusion and protrusion.

Diagnosis: Survey spinal radiographs should be taken to identify degenerative changes typical of a disc herniation and to rule out other causes of the signs. Changes indicative of a disc herniation include narrowing of the intervertebral disc space, narrowing of the intervertebral disc space, narrowing of the intervertebral foramen and the presence of mineralized material within the vertebral canal and disc space (see Chapter 5). A definitive diagnosis with adequate accuracy for surgery to be undertaken cannot be reached with survey radiographs alone and so either CT, myelography or MRI is used to identify the site of spinal cord compression (Figure 14.15). Cerebrospinal fluid (CSF) analysis is performed concurrently to rule out an inflammatory disorder.



**14.15** Lateral cervical myelogram of a dog with disc herniation at C3–C4 (arrowed).

#### Treatment and prognosis:

Conservative management: Dogs can be managed conservatively with strict cage rest for 4 weeks combined with pain relief using anti-inflammatory drugs, opioids or muscle relaxants. Judicious use of antiinflammatory doses of corticosteroids combined with appropriate cage confinement can be attempted if the pain is not responsive to non-steroidal anti-inflammatory drugs (NSAIDs). Muscle spasm can also be responsive to gentle massage and hot packing of the neck or to oral diazepam administration (0.5 mg/kg g8-12h). Administration of an H<sub>2</sub> receptor antagonist such as famotidine or ranitidine may help to prevent the development of gastric ulceration. The aim of cage rest is to allow defects in the annulus fibrosus to heal, and resolution of pain does not mean that confinement should be discontinued. If this approach is successful, gradual reintroduction to controlled exercise can be attempted and in the long term the owners should be cautioned to prevent their pet from activities that involve jumping. Dogs should be monitored weekly: if the pain is unresponsive to conservative therapy or recurs, or if neurological deficits develop, surgery should be recommended.

Surgical management: Indications for surgery include unremitting or severe pain, recurrent pain, or neurological deficits. Once the site of disc herniation has been confirmed, a ventral slot is performed to remove the herniated disc material (see Chapter 21). Adjacent discs are fenestrated to prevent recurrence of the problem. Post-operatively, dogs are provided with pain relief and confined for 4 weeks (2 weeks of strict confinement and then, if doing well, 2 weeks of increasing controlled exercise). Dogs are then gradually reintroduced to normal activity. If the dog has neurological

deficits, postoperative care includes passive range-ofmotion exercises, massage, hydrotherapy and controlled exercise (see Chapter 24).

The prognosis for dogs treated conservatively is unknown. The prognosis for dogs treated surgically is excellent, unless neurological deficits are severe.

#### Synovial cysts

**Clinical signs:** Neurological deficits include spinal hyperaesthesia and signs of a chronic and progressive myelopathy reflecting the site of the lesion.

**Pathogenesis:** Large cysts can develop from the synovial membranes around the articular processes, causing dorsolateral compression of the spinal cord. This can occur as a component of cervical stenotic myelopathy (see above) or be an isolated disorder. Affected dogs are typically either young giant breeds with multiple cysts present in the cervical spine, or older large breeds with single cysts in the thoracolumbar spine (see Chapter 15) (Dickinson *et al.*, 2001).

**Diagnosis:** Degenerative joint disease of the affected articular processes is usually visible on survey radiographs. Extradural lesions causing dorsolateral spinal cord compression are visible on myelography (with or without CT) and on MR images. There are non-specific changes on CSF analysis. The precise nature of the lesion is confirmed at surgery.

**Treatment and prognosis:** The spinal cord can be decompressed by surgical removal of the cysts. This is usually achieved by a dorsal laminectomy in the cervical spine and a hemilaminectomy in the thoracolumbar spine. Prognosis is usually good in uncomplicated cases addressed early.

#### Calcinosis circumscripta (tumoral calcinosis)

*Clinical signs:* Affected dogs show progressive tetraor paraparesis, depending on lesion location.

Pathogenesis: This is an unusual disease of young large breed dogs, such as the German Shepherd Dog and Rottweiler. Mineralization of the ligamentous structures of the vertebral column, usually either dorsal to the atlantoaxial junction (Figure 14.16) or dorsal to the mid thoracic spine causes pain and compression of the spinal cord (Lewis and Kelly, 1990). Both renal disease and trauma are known to cause ectopic mineralization but there is no evidence of either problem in these dogs. Postulated causes include a foreign body reaction to aberrant mesenchymal tissue and an as yet unidentified inherited defect of calcium and phosphate homeostasis (De Risio and Olby, 2000).

**Diagnosis:** Diagnosis can be made from a survey spinal radiograph. Routine blood work should be done, to rule out renal disease and to check calcium and phosphate levels. Parathyroid hormone levels can be measured. Radiography of the limbs should also be done, to identify other sites of soft tissue mineralization.



14.16 Lateral cervical radiograph from a 4-month-old Viszla with calcinosis circumscripta. Note the focus of mineralization dorsal to the atlas (arrowed).

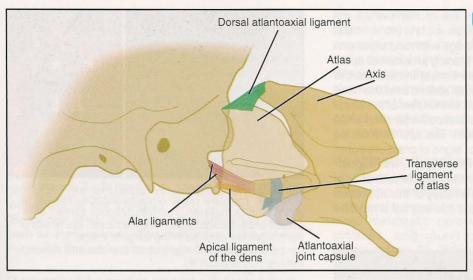
**Treatment and prognosis:** Surgical decompression is recommended and is successful in dogs with single lesions, mild to moderate neurological deficits and no evidence of an underlying cause.

#### **Anomalous diseases**

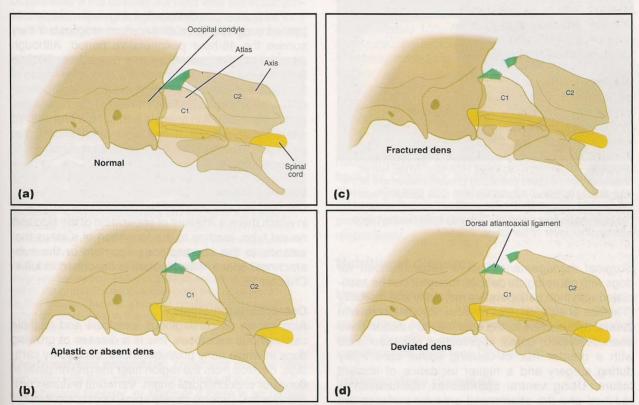
#### Atlantoaxial instability

Clinical signs: Onset of signs in dogs with the congenital form of the disease usually occurs in young animals (<2 years of age), though problems can develop at any age. Signs can develop acutely or gradually, and waxing and waning of signs is often reported – presumably a reflection of instability at the atlantoaxial junction causing repeated injury to the spinal cord. Signs include neck pain (variably present), ataxia, tetraparesis, and postural-reaction and conscious proprioceptive deficits with normal to increased muscle tone and myotatic reflexes in all four legs. In severe cases, animals can present with tetraplegia and difficulty in breathing and they may die acutely as a result of respiratory failure.

Pathogenesis: The atlas (first cervical vertebra) and axis (second cervical vertebra) are bound together by ligaments that run from the dens of the axis to the atlas and the skull, over the dens binding it to the floor of the atlas (the transverse ligament) and between the dorsal lamina of the atlas and the dorsal spinous process of the axis (Figure 14.17). The dens is a bony projection from the cranial aspect of the body of the axis and develops from a separate growth plate. Subluxation of the atlantoaxial junction (Figure 14.18) is a relatively common problem and usually results from a failure of ligamentous support. Toy and small breeds such as Chihuahua and Yorkshire Terrier are at highest risk of the problem as a result of failure of development of the dens (congenital absence or hypoplasia of the dens). Dorsal angulation of the dens can also occur. Fracture of the dens and rupture of the soft tissues maintaining the stability of the atlantoaxial junction can occur in any dog or cat as a result of trauma (Cook and Oliver, 1981).



Ligaments of the atlas and axis vertebrae.



Atlantoaxial subluxation. (a) Normal relationship of axis (C2) to atlas (C1) vertebra and the spinal cord. (b) Subluxation associated with an aplastic or absent odontoid process (dens). Clinical signs may not be severe as there is minimal compression. However, concussion is always possible and can lead to severe motor and sensory dysfunction. (c) Subluxation due to traumatic fracture. Trauma may lead to fracture of the dens but is often associated with ligament rupture. (d) Subluxation associated with a dorsally deviated dens. Compression of the spinal cord can be exacerbated by such a subluxation. (Modified from Wheeler and Sharp, 1994)

Diagnosis: Atlantoaxial subluxation can be diagnosed from survey radiographs of the cervical spine but extreme care must be taken when restraining and moving dogs in which this disease is suspected. If the animal is sedated or anaesthetized, the head and neck should be supported in slight extension to avoid further spinal cord injury. On lateral radiographs an increased space can be seen between the dorsal lamina of the atlas and the dorsal spinous process of the axis. In severe cases, malalignment of the bodies of the atlas

and axis is clearly visible (see Chapter 5). The presence and size of the dens can be evaluated most accurately on ventrodorsal (VD) views. If there is no evidence of subluxation on the lateral views, the neck can be carefully flexed to see if there is instability (the space between the dorsal lamina of the atlas and the dorsal spinous process of the axis should be evaluated). It is preferable to do this with fluoroscopy so that the movement can be monitored, to prevent accidental iatrogenic subluxation.

## Treatment and prognosis:

Conservative management: Dogs with mild signs can be treated conservatively by placing an external splint for at least 6 weeks. The splint must immobilize the atlantoaxial junction and so must extend over the head cranial to the ears and go back to the level of the chest (Figure 14.19). The aim is to stabilize the junction while the ligamentous structures heal. The splint should be checked daily by the owner for signs of pressure sores and checked weekly by the veterinarian, with regular bandage changes if necessary. While often effective in the short term, the long-term efficacy of this approach is not known and dogs treated in this way will always be at risk of repeated injury.



An 8-month-old West Highland White Terrier with a splint placed to prevent movement of the atlantoaxial junction. A thick layer of cast padding was placed first; then a splint was modelled to run ventral to the chin, neck and sternum. This was then held in place with another layer of bandage.

Surgical management: This is recommended for dogs with neurological deficits, though it can be associated with high perioperative morbidity and mortality (Thomas et al., 1991; Beaver et al., 2000). Dorsal and ventral approaches to the atlantoaxial junction have been described; dorsal approaches are associated with a greater risk of causing spinal cord injury during surgery and a higher incidence of implant failure. Using ventral approaches, subluxation is reduced and the atlantoaxial articular surfaces are curetted to promote bony fusion. The two bones are fused using transarticular screws or Kirschner wires and a cancellous bone graft is placed over the junction (Figure 14.20). In the case of a traumatic injury or poor bone purchase, screws or Kirschner wires are placed in the body of the atlas and axis and the junction is stabilized with polymethylmethacrylate cement. A neck splint is placed postoperatively while fusion occurs. This is a problematic area to repair surgically; bone quality is often poor, the bones are small, movement of the vertebrae may cause additional injury to the spinal cord, and the pharynx and larynx can be damaged during retraction. There is a risk of respiratory arrest and death in the perioperative period as a result of additional spinal cord injury, or inflammation of the upper airways secondary to retraction.





Lateral cervical radiograph of a 1-year-old Yorkshire Terrier showing surgical repair of an atlantoaxial subluxation. Two transarticular screws were placed once the subluxation was reduced. The heads of the screws are arrowed in the surgical image. A cancellous bone graft was placed over the articulation between C1 and C2(\*\*).

This is a serious disease but dogs with mild deficits treated surgically have an excellent prognosis if they survive the 48-hour perioperative period. Although reported surgical success rates range from 50% to 90%, the majority report a mortality rate in the region of 20%, with most deaths occurring either during or immediately after surgery. As with all spinal cord diseases, prognosis is worse in animals with severe and chronic neurological deficits. It has also been shown that prognosis is better in young dogs (< 24 months) (Beaver *et al.*, 2000).

#### **Dermoid sinus**

Dermoid sinuses are inherited developmental defects in which there is a failure of separation of the skin and neural tube, leading to the formation of a sinus that extends to the supraspinous ligament or the subarachnoid space. This disease is described in full in Chapter 15.

### Osteochondromatosis

Also known as cartilaginous exostosis and multiple cartilaginous exostoses, this is a disease of growing dogs in which bony protruberances, capped by cartilage, develop from the region near the growth plate of bones of endochondral origin. Vertebral lesions commonly arise, causing severe spinal cord compression. This disease is described in full in Chapter 15.

#### Syringohydromyelia

Clinical signs: Neurological signs are caused by progressive expansion of the cavities and relate to their location. A prominent sign in affected Cavalier King Charles Spaniels is persistent flank scratching with apparent pain in the neck, facial and shoulder region. Torticollis and scoliosis have also both been reported in association with the problem and are thought to result from denervation of local epaxial spinal musculature due to destruction or compression of spinal cord grey matter (Bagley et al., 1997).

**Pathogenesis:** Syringomyelia is a fluid-filled cavity within the spinal cord; hydromyelia is simply dilation of

the central canal. As it can be difficult to differentiate between the two conditions based on imaging studies, the term syringohydromyelia is often used. Both conditions can be a secondary long-term complication of any spinal cord disease, especially those in which a large volume of spinal cord tissue becomes necrotic. Any disease that causes obstruction of normal CSF flow within the spinal cord can result in syringohydromyelia and as such it can be seen in association with neoplasia, in particular intra-axial tumours, and in feline infectious peritionitis (FIP), associated with ependymitis. Cervical syringohydromyelia also occurs as a component of congenital anomalies such as Chiari-type malformations in the Cavalier King Charles Spaniel (Rusbridge et al., 2000) and other small dog breeds such as Pomeranians. The author has seen several Pugs with thoracolumbar syringohydromyelia.

**Diagnosis:** If the cavities connect with the subarachnoid space, myelography may be diagnostic, but they are most reliably seen on MR images (Figure 14.21).



Sagital T2-weighted MR image of the cervical spinal cord and caudal fossa of a 9-month-old Cavalier King Charles Spaniel. The dog presented with persistent neck scratching and mild left-sided deficits. The cerebellar tonsils are herniating through the foramen magnum (arrowed). There is a large accumulation of CSF within the cranial cervical spinal cord that appears white on this image. There is a smaller dilation of the central canal (hydromyelia) in the caudal cervical spinal cord (arrowheads).

Treatment and prognosis: Treatment may be conservative with anti-inflammatory doses of prednisolone and physical therapy, or surgical if there is an underlying cause that can be addressed, such as occipital dysplasia. There is relatively little information available on prognosis, reflecting the recent recognition of this disease with the advent of MRI. Prognosis depends on the severity of signs and whether an underlying cause can be addressed. Successful outcomes have been reported with surgical management of Chiari-like malformations.

#### Vertebral and spinal cord anomalies

Atlantoaxial subluxation is the most common consequence of a vertebral anomaly that causes tetraparesis and this condition was addressed earlier in this chapter. Other vertebral anomalies include: hemivertebrae; transitional, block and butterfly vertebrae; congenital spinal stenosis (often a component of cervical stenotic myelopathy); and vertebral facet dysplasia. These diseases

are considered in full in Chapters 5 (radiographic appearance) and 15. Syringohydromyelia is a common anomalous spinal cord disease causing tetraparesis and is described in the previous section. Other congenital spinal cord diseases include spina bifida, myelodysplasia and spinal dysraphism; they are described in full in Chapter 15. Anomalous diseases affecting the cauda equina specifically, such as sacrocaudal dysgenesis, are considered in Chapter 18.

## **Neoplastic diseases**

Neoplasia can cause pain and tetra- or paraparesis, depending on the location of the lesion. In dogs, extradural tumours (e.g. primary or metastatic sarcomas, metastatic carcinomas and phaeochromocytomas, and round cell tumours) account for approximately 50-60% of spinal tumours, intradural tumours (meningiomas and nerve sheath tumours) account for approximately 30% and intramedullary tumours (e.g. gliomas and ependymomas) account for approximately 10% (Prata, 1977). In cats, the most common spinal tumour is lymphoma. Spinal lymphoma is usually extradural and more likely to occur in the thoracolumbar spine, but can occur in the cervical spine and may infiltrate the brachial plexus (Spodnick et al., 1992; Lane et al., 1994). Neoplasia is more likely to affect older animals and can produce signs by direct compression of the spinal cord, infiltration and destruction of the spinal cord parenchyma, intraparenchymal haemorrhage or by inducing pathological vertebral fractures. Diagnosis, treatment and prognosis of neoplasia affecting the vertebrae and spinal cord are addressed in detail in Chapter 15. Chapters 22 and 23 provide further detail of chemotherapy and radiotherapy, respectively.

## **Nutritional diseases**

#### Hypervitaminosis A

This disease, also known as deforming cervical spondylosis, affects cats that are fed a pure liver diet and is therefore extremely rare in these days of manufactured diets (see Chapter 13).

## Inflammatory diseases

## Discospondylitis

Infection of the intervertebral disc and adjacent vertebral endplates by bacterial or fungal organisms is a common cause of spinal hyperaesthesia in dogs (cats are rarely affected). If left untreated, spinal cord dysfunction can occur as a result of either local inflammation, compression from herniated infected disc material or local abscess formation, or pathological vertebral fracture. Discospondylitis can affect any site in the spine and caudal cervical lesions are common. Because the most common presenting sign is spinal hyperaesthesia, diagnosis, treatment and prognosis of discospondylitis are covered in Chapter 13.

## Spinal empyema

Epidural empyema is a rare but important cause of spinal cord disease. Local bacterial infection of the

epidural fat results in accumulation of purulent material causing compression and inflammation of the adjacent spinal cord. This can be a result of local extension of infection from discospondylitis or a cat bite abscess, or can result from haematogenous spread. In humans, it is also reported as a complication of spinal surgery and epidural catheter placement. Characteristic signs are a high fever, acute progressive spinal hyperaesthesia and progressive myelopathy, with the neurological deficits reflecting the site of infection. The diagnosis and treatment of this disease are described in Chapter 15.

## Meningoencephalomyelitis

Inflammatory conditions of the meninges and the central nervous system can cause tetraparesis as a result of involvement of the brainstem or the spinal cord. Typically signs are multifocal, but any inflammatory or infectious CNS disease can cause focal signs of spinal cord disease. Examples of infectious or inflammatory diseases of the CNS that can cause focal signs of spinal cord disease include FIP, canine distemper, fungal infections (in particular *Cryptococcus neoformans*), the protozoal infections *Neospora caninum* and *Toxoplasma gondii*, rickettsial infections and granulomatous meningoencephalomyelitis (GME). These diseases are diagnosed by analysis of CSF in combination with appropriate titres. They are considered in full in Chapters 10 and 15.

## Steroid-responsive meningitis-arteritis (SRMA)

The predominant manifestation of SRMA is severe spinal hyperaesthesia and this disease is therefore described in full in Chapter 13. With chronic severe disease, neurological deficits (ataxia, para-or tetraparesis) can be present as a result of concurrent myelitis, but this is unusual (Cizinauskas *et al.*, 2000).

## Idiopathic diseases

#### **Arachnoid cysts**

Arachnoid cysts are focal accumulations of CSF within the subarachnoid space. The term cyst is somewhat misleading, as frequently cyst walls are not evident. Accumulation of CSF over time causes progressive compression of the spinal cord and neurological deficits related to the site of compression.

Clinical signs: Arachnoid cysts occur most commonly in young large dog breeds (e.g. Rottweiler) dorsal to the cranial cervical spinal cord, and in older smaller breeds (e.g. Pug) dorsal to the thoracolumbar spinal cord (see also Chapter 15), though cysts can occur at any site, at any age and in any breed of dog. Onset of signs (tetraparesis, paraparesis, ataxia) is typically chronic and it is notable that dogs can present with faecal or urinary incontinence as an early sign (Skeen et al., 2003). Neck pain may be present.

**Pathogenesis:** The aetiology of these cysts is most likely multifactorial with inherited predisposition, trauma and arachnoiditis all postulated to play a role (Dyce *et al.*, 1991).

**Diagnosis:** Survey radiographs are unremarkable. Cysts are identified as a focal accumulation of contrast medium in the subarachnoid space, or an intradural filling defect on myelography (Figure 14.22). They are also visible as an accumulation of fluid in the subarachnoid space on MR images.



Lateral cervical myelogram of a 1-year-old Labrador Retriever. The subarachnoid space is markedly dilated over C3 because of an arachnoid cyst.

Treatment and prognosis: Recommended treatment in dogs with neurological deficits is surgical decompression by removal or fenestration and marsupialization of cysts. Conservative management may improve a small proportion of dogs but is only recommended in animals with mild neurological deficits. Conservative management includes controlled exercise and anti-inflammatory doses of prednisolone. Animals should be monitored regularly and surgery recommended if deterioration occurs.

The prognosis for dogs treated surgically depends on the severity and duration of clinical signs and the age of the dog. Young dogs with mild signs have an excellent short-term prognosis (< 1 year). Signs may recur in approximately one-third of dogs in the longer term (Skeen *et al.*, 2003).

#### Toxic diseases

#### **Tetanus**

Clinical signs: Presenting signs include a generalized increase in extensor tone manifesting as a stiff stilted gait, raised tail and a characteristic facial expression ('risus sardonicus') resulting from an increase in facial muscle tone. The palpebral fissure is wider than usual, the pupils are miotic, the ears rigid, the lips drawn back and the forehead is wrinkled. The third eyelid may be protruded and there is often profuse salivation because of difficulty swallowing. Visual and tactile stimuli, and placing the animal on its side, often result in a further increase in muscle tone, producing muscle spasms (Coleman, 1998). As signs progress, the animal may become recumbent, have difficulty breathing and can develop a hiatal hernia and megaoesophagus as a result of increased diaphragmatic tone. Both bradycardia and tachycardia have been described in dogs with

tetanus, due to effects of the toxin on the autonomic nervous system. Cats are more likely to present with a focal form of the disease, with signs limited to the area of the infection, e.g. monoparesis following a distal limb injury, though this has also been reported in dogs (Malik *et al.*, 1989).

Pathogenesis: Tetanus is caused by absorption of tetanus toxin (tetanospasmin) produced by the anaerobic bacteria Clostridium tetani. The source of the bacterium is usually a penetrating wound or failure of sterile surgical technique providing both contamination with clostridium and the conditions suitable for its growth (Bagley et al., 1994). The toxin is absorbed into the bloodstream and from there is taken up by nerves. In a similar fashion to botulinum toxin, tetanospasmin prevents presynaptic release of neurotransmitter. However, in tetanus the toxin is transported retrogradely up motor neurons and from there to inhibitory interneurons, where it blocks release of the inhibitory neurotransmitters glycine and gammaaminobutyric acid (GABA). As a result, there is loss of inhibition of motor neurons, causing a state of rigidity, with superimposed muscle spasms with stimulation. Although both species can develop clinical signs, dogs are more susceptible to tetanospasmin than cats (Coleman, 1998).

Diagnosis: The diagnosis is usually presumptive and based on the presence of classic clinical signs. The presence of a wound or history of recent surgery are supportive of the diagnosis: attempts can be made to culture the organism but are frequently unsuccessful, due to low organism numbers and the need for anaerobic conditions. An infectious process may be suggested by a complete blood cell count, and CK concentrations are often increased due to the increased muscle tone. CSF analysis is unremarkable, nerve conduction studies are normal, but electromyography (EMG) may show prolonged spontaneous motor unit potentials following needle insertion. This can be especially helpful in diagnosing mild or focal forms of the disease. Antibodies to the tetanus toxin can be measured by some laboratories.

Treatment and prognosis: If the source of infection can be identified it should be treated by surgical debridement (if necessary), flushing with hydrogen peroxide and intravenous administration of penicillin G (20,000-100,000 U/kg q6-12h). Metronidazole, tetracycline and ampicillin are alternative choices of antibiotic if penicillin G is not available. Antitoxin should be administered intravenously over 10 minutes (100-500 IU/kg, but a wide range of doses is cited by different authors) to inactivate any circulating toxin. A test dose of 0.1 ml should be given subcutaneously 20-30 minutes prior to the intravenous dose, to check for adverse reactions. Extensor tone can be reduced with a number of different drugs: phenobarbital, pentobarbital, acepromazine, chlorpromazine, diazepam and methocarbamol have all been advocated. If unable to prehend and swallow food, the animal may need to have a gastrostomy

tube placed. The animal should be turned regularly and the environmental stimuli kept to a minimum. Bladder expression or catheterization may be necessary. Recovery is slow and signs may take up to 4 months to resolve completely, though most animals are dramatically improved within 1 month of starting treatment. In a review of 55 cases of tetanus in the dog (Mason, 1964), 58% recovered, but the recovery rate is probably higher now due to improvements in medical care.

## **Traumatic diseases**

#### Spinal cord contusion and traumatic disc herniation

**Clinical signs:** Signs reflect the site of injury and can be multifocal. A careful neurological examination is therefore vital.

Pathogenesis: Traumatic injuries (e.g. road traffic accidents, falling from a height, horse kicks) often result in spinal cord injuries, usually with associated vertebral fractures and luxations. Sometimes animals suffer an obvious traumatic event (either witnessed, or with other external evidence), associated with acute onset of focal signs of spinal cord dysfunction with no evidence of a vertebral fracture or luxation. It is possible for sudden flexion or extension or axial loading of the vertebral column to occur without causing fractures or permanent luxations, but causing contusions to the spinal cord, focal haemorrhages or traumatic disc herniations. In the case of cats and nonchondrodystrophoid breeds of dog, the herniated nucleus pulposus is often not mineralized and therefore causes a primarily concussive injury, with little or no compression.

Diagnosis: This is a presumptive diagnosis in the face of compatible history and clinical findings, with no evidence of vertebral facture or luxation on survey radiographs and CT images or myelography. The patient should be handled with extreme care until survey radiographs rule out the presence of an unstable vertebral fracture or luxation. The atlantoaxial junction should be evaluated very carefully, as this site is predisposed to injury. A collapsed disc space and focal extradural compression may indicate a traumatic disc herniation and focal swelling of the spinal cord may be present. MRI will identify focal oedema within the spinal cord and may reveal changes in the nucleus pulposus indicating herniation.

Treatment and prognosis: The protocols for medical management of acute spinal cord injuries with methylprednisolone sodium succinate are described in Chapter 19. If there is significant compression of the spinal cord by herniated disc material, decompressive surgery may be indicated. Management of the patient focuses on treatment of any other injuries, and rehabilitation (see Chapter 24). Prognosis depends on the severity of injury: it is guarded in the tetraplegic patient with associated hypoventilation, but good if there is any motor function present.

#### Cervical vertebral fractures and luxations

Clinical signs: Neurological deficits reflect the site of the injury but, as a result of the relatively spacious vertebral canal in the cervical region, quite dramatic luxations can be associated with only minimal neurological deficits and pain (Stone et al., 1979; Hawthorne et al., 1999). It is not uncommon for neurological deterioration to occur days after the traumatic incident as a result of instability secondary to a fracture (Hawthorne et al., 1999). It is therefore important to obtain good quality cervical radiographs in any animal in which head and neck trauma are suspected (Olby et al., 2002).

**Pathogenesis:** Vertebral fractures and luxations can result from pathological processes such as vertebral neoplasia and discospondylitis, but most commonly result from external trauma. Cervical vertebral injuries are less common than thoracolumbar injuries (Selcer et al., 1991) but the atlantoaxial junction is relatively unstable (see atlantoaxial instability, above) and therefore particularly at risk. The axis is the most commonly fractured cervical vertebra because it acts as a fulcrum between the caudal cervical spine and the so-called cervicocranium (the skull, atlas, dens and body of the axis) (Stone et al., 1979).

Diagnosis: Extreme care should be taken when evaluating these animals to avoid exacerbating injuries due to vertebral instability. Initial management of the critical patient is covered in Chapter 19. A careful physical and neurological examination should be completed and stabilization of the patient undertaken if indicated. Lateral survey radiographs of the entire spine should be obtained. If there is no evidence of a vertebral fracture or luxation on the lateral views, the animal can be placed carefully on its back to obtain ventrodorsal projections of the spine (Chapter 5), or horizontal beam views can be obtained. The timing and type of further imaging indicated will depend on the neurological status of the animal and the radiographic findings but include CT scanning, myelography and MRI. Myelography or MRI is indicated if the clinical findings do not match the survey radiographic findings. CT of lesions identified on survey radiographs is appropriate if the radiographic and clinical findings are in agreement, to obtain good anatomical detail of the bone lesions and relative displacement of bone fragments. However, if the owner does not want spinal surgery to be performed (for financial or other reasons), further imaging will not usually help with case management. Also, the animal may have other medical problems that preclude anaesthesia at that time (e.g. cardiac arrhythmias secondary to trauma).

**Treatment and prognosis:** Treatment can be conservative or surgical. Conservative treatment includes placement of an external splint (in the case of unstable fractures or luxations), cage confinement, provision of analgesia and nursing care, and rehabilitation

(see Chapter 24). Conservative management is appropriate in cases with mild neurological deficits, minimally displaced fractures/luxations or no evidence of spinal cord compression. Splints should be placed on animals with evidence of vertebral instability (see also Chapters 15 and 19) so as to prevent movement of the caudal cervical spine and the atlantoaxial junction. Correct splint placement is described in the section on atlantoaxial instability (see Figure 14.19). Surgical treatment is indicated in cases with severe neurological deficits or pain and evidence of compression or vertebral instability on imaging. Aims of surgery are to realign, stabilize and decompress the spinal cord and intervertebral foraminae (to prevent persistent nerve root pain). Stabilization is usually achieved by the placement of screws or pins in the vertebral bodies with application of polymethylmethacrylate cement around their protruding heads (see Figure 14.20) but plates can also be used. A full discussion of surgical techniques is beyond the scope of this book and can be found in surgical texts (Wheeler and Sharp, 1994; Slatter, 2002).

Prognostic factors have been evaluated in 56 dogs with cervical vertebral fractures (Hawthorne et al., 1999). Non-ambulatory tetraparesis and prolonged interval from trauma to referral (> 5 days) were associated with a worse outcome. Prompt identification and referral of these cases is therefore important. In dogs undergoing surgery, perioperative mortality was relatively high (4 of 11 dogs suffered cardiopulmonary arrest). This may reflect the need for ventilatory support in severely injured dogs, particularly if surgery is associated with further inadvertent iatrogenic damage. In the same study, 37 of 40 dogs managed conservatively recovered, indicating that the prognosis for recovery is good in dogs in which surgery is not indicated. Dogs with severe spinal cord injuries (tetraplegia) that require ventilatory support have a worse prognosis.

#### Vascular diseases

## Spinal haemorrhage

**Clinical signs:** The clinical signs reflect the side of the haemorrhage and are acute in onset. They can be multifocal.

Pathogenesis: Bleeding disorders can be inherited (e.g. von Willebrand's disease) or acquired secondary to rodenticide toxicity or infectious/inflammatory diseases (e.g. immune-mediated thrombocytopenia, disseminated intravascular coagulation). Indeed, tickborne infectious causes of vasculitis and thrombocytopenia, such as Rocky Mountain spotted fever, are common in some parts of the world. Haemorrhage into the CNS can occur with any bleeding disorder and, although unusual, it can be the first manifestation of the disease. For example, epidural haemorrhage causing spinal cord compression has been reported in Dobermann Pinschers with von Willebrand's disease (Applewhite et al., 1999). The presence of

petechiae, ecchymoses or prolonged bleeding following venipuncture should alert the veterinarian to the possibility of a bleeding disorder. It is not unusual to find extensive extradural haemorrhage at the site of acute intervertebral disc herniations or vertebral fractures and luxations. These animals do not have an underlying coagulopathy; the haemorrhage has occurred as a direct result of disruption of the venous sinuses that overlie the disc.

Diagnosis: The history and clinical findings may be suggestive of a bleeding disorder. A buccal mucosal bleeding time can be performed to evaluate platelet function by gently tying the upper lip back with gauze to expose the mucosa, and then making parallel cuts 1 mm deep and 5 mm long with a blade and noting the time taken for bleeding to stop. Devices specifically designed to make these cuts are available commercially. Blood can be carefully blotted away as it runs down the gum, but the incision should not be touched. Bleeding times > 4.5 minutes are abnormal but there is a lot of individual variation (Mever et al., 1992). If rodenticide toxicity is suspected, activated clotting time (ACT) should be measured. Values >120 seconds are supportive of a coagulopathy. Further evaluation of clotting function includes a manual platelet count, one-stage prothrombin time (OSPT) and activated partial thromboplastin time (APTT). The levels of individual clotting factors can be measured by specialist laboratories.

If a bleeding disorder is not suspected, a routine work-up for focal spinal cord signs should be undertaken. Survey radiographs are unremarkable, and CSF may be diffusely haemorrhagic if the haemorrhage is intraparenchymal. If haemorrhage is extradural, it will be visible as a large mass on myelography and is readily identifiable on CT images if it occurred in the preceding 24 hours. MRI will detect both recent and old haemorrhages but the appearance changes with time (Thomas, 1996). If a haemorrhage is suspected based on imaging, surgery should not be undertaken unless the coagulation profile is normal.

**Treatment and prognosis:** Treatment is specific to the cause. For example, rodenticide toxicity can be treated with vitamin K1 (2.5–5 mg/kg s.c., then 0.25–5mg/kg orally, divided q8–12h for 5 days to 5 weeks, depending on the product involved) and a plasma or whole-blood transfusion if the patient is actively bleeding. Prognosis depends on the underlying aetiology and the severity of neurological dysfunction caused.

#### Fibrocartilaginous embolism

Clinical signs: Fibrocartilaginous embolism (FCE) causes peracute onset of non-painful neurological deficits, most commonly in the lumbosacral intumescence (see Chapter 15) but also in the brachial intumescence. Affected dogs are usually young and of large non-chondrodystrophoid breeds, engaged in exercise at onset of signs, but smaller breeds such as Shetland Sheepdogs, Miniature Schnauzers and

Yorkshire Terriers can be affected and are more likely to have signs localizing to the sixth cervical to second thoracic spinal cord segments. Signs are often dramatically lateralized, producing hemiparesis. Involvement of the sympathetic tracts in the cervical spinal cord can result in Horner's syndrome and vasodilation on the affected side. The vasodilation produces differential hyperthermia that can be detected by comparing the temperature in the front feet and comparing the external pinnae (which will be flushed on the affected side) (Griffiths, 1970). FCE rarely occurs in cats but there is one report of a cervical FCE (Abramson et al., 2002).

**Pathogenesis:** FCE is a syndrome in which fibrocartilage identical to that found in the nucleus pulposus embolizes to the spinal cord vasculature, producing an area of ischaemic necrosis centred on the spinal cord grey matter (Cauzinille and Kornegay, 1996). Signs are often lateralized, as the embolus usually lodges in one branch of the ventral spinal artery. For a discussion of the aetiology of FCE, see Chapter 15.

Diagnosis: FCE should be suspected in animals presenting with peracute onset of lateralizing signs in the absence of spinal pain. Cervical disc herniations as a result of trauma can produce a similar syndrome, with dramatic lateralization of signs and differential hyperthermia, but these animals usually have neck pain. Survey spinal radiographs are unremarkable and there is no evidence of spinal cord compression on myelography, though occasionally focal swelling of the cord is detected (see Chapter 5). The infarcted area is visible on MR images. CSF analysis may reveal disproportionately elevated protein and a neutrophilic pleocytosis.

**Treatment and prognosis:** Treatment centres around successful rehabilitation of the animal (see Chapter 24). Improvement can be dramatic over the first 7 days and will continue for 1–3 months after injury.

The extent of recovery will depend on the extent of injury. If deep pain perception is preserved in the thoracic and pelvic limbs on the affected side, the prognosis is good. If deep pain perception is absent in one or more limbs, the prognosis is more guarded, but deep pain perception should be monitored weekly: its reappearance indicates the potential for recovery. The author has seen dogs that did not regain deep pain perception or use of the thoracic limb on the affected side, but recovered full use of their other three legs and were able to walk without problem.

## Miscellaneous vascular diseases

Focal spinal cord deficits can be caused by emboli as a result of extreme hyperlipaemia (inherited in Miniature Schnauzers or associated with hypothyroidism), vegetative valvular disease (e.g. secondary to endocarditis) and neoplasia. A variety of different focal neurological deficits have been reported with extreme polycythaemia and leukaemia as a result of sludging of blood vessels.

## Lower motor neuron disease

Lower motor neuron diseases that can cause tetraparesis are listed in Figure 14.23.

Mechanism of disease	Specific diseases	
Degenerative	Inherited peripheral neuropathies: motor, sensorimotor, sensory, metabolic [14] Inherited myopathies [17] Inherited junctional disease [17]	
Metabolic	Diabetes mellitus [14] Hypothyroidism [14, 17] Hyperthyroidism [17] Hypoadrenocorticism [17] Hyperadrenocorticism [14] Metabolic myopathies [17]	
Neoplastic	Paraneoplastic – insulinoma, other [14]	
Idiopathic	Distal denervating disease [14]	
Inflammatory	nflammatory Chronic inflammatory demyelinating polyneuropathy [14] Ganglioradiculitis [14] Myasthenia gravis [17] Polyradiculoneuritis: infectious (protozoal); immune-mediated [14] Polymyositis: infectious; immune-mediated [1	
Toxic Botulism [14] Drug-induced [14] Tick paralysis [14]		

Lower motor neuron diseases that can cause tetraparesis. The numbers in square brackets denote the Chapters in which the conditions are discussed in detail.

## **Degenerative diseases**

## Breed-specific neuropathy

Inherited and breed-related neuropathies are rare diseases that usually affect young animals and can produce generalized motor, mixed motor and sensory, pure sensory and/or autonomic deficits (Figure 14.24) (see Chapter 18 for discussion of dysautonomia).

Motor and mixed sensorimotor neuropathies: This group of diseases includes the motor neuron diseases (in which the motor neurons in the ventral horn of the spinal cord degenerate), axonopathies, demyelinating diseases and distal neuropathies. Typically progressive LMN paresis develops, often affecting the pelvic limbs first but eventually involving the thoracic limbs. The concurrent development of laryngeal paralysis and megaoesophagus is recognized as a syndrome called laryngeal paralysis polyneuropathy (LPP) complex. This syndrome has been reported in young Rottweilers, Dalmatians and Pyrenean Mountain dogs (Braund, 2003b) and some adult dogs with idiopathic laryngeal paralysis also suffer from a more generalized neuropathy. Although many different breeds have been reported with these disorders (see Appendix), most are extremely rare and are reviewed in detail elsewhere (Braund, 2003b; Summers et al., 1995b).

Disease	Breed
Dogs	
Giant axonal neuropathy	German Shepherd Dog
Globoid cell leucodystrophy	West Highland White Terrier; Cairn Terrier; Irish Setter
Hypertrophic neuropathy	Tibetan Mastiff
Polyneuropathy	Alaskan Malamute
Laryngeal paralysis polyneuropathy complex	Dalmatian; Pyrenean Mountain Dog; Rottweiler
Sensory neuropathy	Border Collie; English Pointer; Longhaired Dachshund
Progressive axonopathy (sensory)	Boxer
Distal sensorimotor polyneuropathy	Rottweiler; Great Dane; Chesapeake Bay Retriever; St Bernard; Collie; Labrador Retrieve Newfoundland
Motor neuron disease	Brittany Spaniel; Swedish Lapland Dog; English Pointer; Great Dane/ Bloodhound or St Bernard cross; German Shepherd Dog; Dobermann Pinscher; Griffon Briquet Saluki; Rottweiler
Cats	DE CARROLL MANAGEMENT
Hyperchylomicronaemia	Domestic Short-hair; Domestic Long-hair; Siamese; Persian; European; Himalayan
Hyperoxaluria	Domestic Short-hair
Distal polyneuropathy	Birman
Niemann-Pick disease subtype A	Siamese
Glycogenosis type IV	Norwegian Forest

14.24 Inherited peripheral neuropathies.

Sensory neuropathies: Familial sensory neuropathies are particularly unusual but have been reported in English Pointers (Cummings et al., 1981) and Longhaired Dachshunds (Duncan and Griffiths, 1982) with sporadic reports in other breeds of dog, such as the Border Collie. Dachshunds present with nociceptive deficits, mild ataxia and loss of conscious proprioception. These dogs have been reported to self-mutilate their penis and dribble urine. The disease in English Pointers is more severe and more specific to nocioception. They lose nocioception in their distal limbs at around 3–8 months of age and as a result lick, chew and even autoamputate their digits. These dogs do not have conscious proprioceptive deficits.

Inherited metabolic disorders: Certain storage diseases (e.g. Niemann–Pick disease in cats; globoid cell leucodystrophy in Cairn and West Highland White

Terriers and Irish Setters) (Fletcher et al., 1966; Cuddon et al., 1989; McDonnell et al., 2000) cause a peripheral neuropathy in addition to CNS signs. Other inherited metabolic disorders that cause generalized peripheral neuropathies in cats include hyperchylomicronaemia (Jones et al., 1986) and hyperoxaluria (Blakemore et al., 1988). As hyperchylomicronaemia is encountered in Siamese, Domestic Short- and Longhair, Persian and Himalayan breeds of cat, it merits further description. This disease is the result of a mutation in the gene encoding the enzyme lipoprotein lipase and is inherited as an autosomal recessive trait (Watson et al., 1992). The resultant fasting hyperchylomicronaemia is associated with the development of focal xanthomata. These are granulomatous masses believed to represent organizing haematomas comprising macrophages, cholesterol and triglyceride crystals, haemosiderin and lipofuscin. They are more likely to develop over pressure points that are more susceptible to trauma. Affected cats develop a variety of neuropathic signs as a result of compression of peripheral nerves by these xanthomata. The specific neurological deficits vary between individuals, reflecting the location of xanthomas, but typically include LMN mono-, para- or tetraparesis and cranial nerve deficits. Signs usually develop after 8 months of age and can be reversed by feeding a low-fat, high-fibre diet.

Diagnosis: Diagnosis is by recognition of typical breed, age of onset and presentation and by ruling out other disorders by electrophysiological evaluation of nerve function and nerve biopsy (see Chapters 4 and 6). Hyperchylomicronaemia in cats is diagnosed by the presence of fasting hyperlipaemia, measurement of the lipid profile (elevated chylomicrons, cholesterol and triglycerides and mild elevation in very low density lipoproteins) and measurement of lipoprotein lipase activity. Fundic examination sometimes reveals lipaemia retinalis. There is a genetic test for the mutation that causes globoid cell leucodystrophy in Irish Setters and West Highland White and Cairn Terriers (Victoria et al., 1996; McDonnell et al., 2000).

Treatment and prognosis: Therapy is limited to symptomatic management of signs in most diseases, including laryngeal tie-back in dogs with upper airway obstruction secondary to larvngeal paralysis and physical therapy to maintain range of motion and muscle mass (see Chapter 24). One exception is hyperchylomicronaemia in cats, which can be treated successfully by feeding a low-fat, high-fibre diet. It is important to recognize the problems and diagnose the cause of signs in animals used for breeding. Reported syndromes are listed in Figure 14.24 and in Appendix 1.

#### Metabolic diseases

#### **Endocrine neuropathy**

Endocrine diseases that are known or suspected to cause a peripheral neuropathy include diabetes mellitus, hypoglycaemia (as a result of insulinoma in dogs), hypothyroidism and hyperadrenocorticism.

Diabetes mellitus: Poorly controlled diabetes mellitus causes distal axonal degeneration, with the longest peripheral nerves affected first. The most common manifestation of this problem is a sciatic neuropathy in cats causing a plantigrade stance in the pelvic limbs at rest and when walking (Figure 14.25) (Kramek et al., 1984). Affected cats retain the ability to walk but hock flexion is absent when the withdrawal reflex is tested. Although pathological changes and sporadic cases of neuropathy have been detected in diabetic dogs, it is usually a subclinical problem in this species. Diagnosis is strongly suspected in animals with poorly controlled diabetes and classic neurological findings. Definitive diagnosis is made by electrophysiological studies and nerve biopsy. Although axonal degeneration can be present in severely affected animals, the most common finding is abnormalities in Schwann cells and myelin (Mizisin et al., 2002). Prognosis for full recovery of peripheral nerve function is guarded, but restoring normoglycaemia prevents progression and in mild cases may result in complete resolution of neurological signs (Kramek et al., 1984).



14.25

The typical stance of a cat with sciatic neuropathy associated with diabetes mellitus.

Hypothyroidism: This can be associated with generalized weakness as a result of a peripheral neuropathy. In addition, idiopathic neuropathies such as facial or laryngeal paralysis, peripheral vestibular syndrome and megaoesophagus have been linked to hypothyroidism but the exact relationship between these neuropathies and hypothyroidism remains unclear (Jaggy et al., 1994). Diagnosis of hypothyroidism is made by measurement of serum total and free T4 and TSH levels. Supplementation with thyroxine may reverse signs of generalized peripheral neuropathy over 2-3 months but laryngeal and oesophageal abnormalities usually persist.

Hyperadrenocorticism: A peripheral neuropathy has been reported in dogs with hyperadrenocorticism but is a rare complication of this disease and is more commonly a subclinical disorder.

## Neoplastic diseases

#### Insulinoma

Chronic, severe hypoglycaemia (< 3 mmol/l) is almost invariably associated with insulinomas in dogs. The most common neurological signs result from the effects of hypoglycaemia on the CNS (seizures, weakness, exercise intolerance and collapse). Persistent hypoglycaemia may also cause a distal peripheral neuropathy that manifests initially as a stiff gait, particularly in the pelvic limbs, but progresses to more obvious signs of a generalized peripheral neuropathy with prominent sciatic deficits (Chrisman, 1980; Braund et al., 1987a). This paraneoplastic neuropathy has also been identified in ferrets with insulinomas. Treatment of the insulinoma may improve the gait, depending on the extent of the underlying disease.

#### Paraneoplastic neuropathy

Paraneoplastic peripheral neuropathies are well recognized in humans in association with particular types of cancer but infrequently recognized in dogs and cats. With the exception of the neuropathy associated with insulinomas in dogs (see below), there are only sporadic reports of neuropathies associated with a variety of different cancers such as bronchogenic and mammary carcinoma and multiple myeloma (Braund *et al.*, 1987b; Villiers and Dobson, 1998; Mariani *et al.*, 1999). Treatment of the primary neoplasia may result in an improvement in signs due to the neuropathy (Villiers and Dobson, 1998; Mariani *et al.*, 1999).

## Idiopathic diseases

## Distal denervating disease

This is reportedly a common peripheral neuropathy in the UK but it has not been recognized elsewhere. The aetiology of this disease is unknown but, as the name implies, the terminal and intramuscular branches of motor nerves degenerate, producing progressive tetraparesis that is first evident in the pelvic limbs (Griffiths and Duncan, 1979). Weakness progresses over days to weeks to LMN tetraplegia and dysphonia, and severe muscle atrophy develops. Diagnosis is by electrophysiological studies (EMG shows that denervation and nerve conduction studies are abnormal). Biopsies are not helpful except to rule out other diseases, as the lesion is usually distal to the biopsy site. Treatment involves supportive care and the prognosis is excellent if adequate nursing care can be given.

## Inflammatory diseases

# Chronic inflammatory demyelinating polyneuropathy

Clinical signs: Chronic inflammatory demyelinating polyneuropathy (CIDP) causes slowly progressive LMN tetraparesis in adult dogs and cats with no gender or breed bias (Cummings and de Lahunta, 1974; Shores et al., 1987; Braund et al., 1996). Signs can relapse intermittently and can progress to tetraplegia. Shifting lameness, a plantigrade stance and

ventroflexion of the neck have been described in cats, along with megaoesophagus and regurgitation. Leg tremors and laryngeal and facial paralysis have been noted in dogs.

**Pathogenesis:** This is an apparently immune-mediated disease in which the inflammatory reaction is focused on peripheral nerve myelin sheathes. The aetiology of the disease is unknown but it appears to be similar to chronic inflammatory demyelinating polyneuropathy in humans.

*Diagnosis:* Diagnosis is reached by a combination of electrophysiological studies and nerve biopsy. Typically, motor nerve conduction velocity is reduced. There is multifocal paranodal demyelination in teased nerve fibre preparations, and thinly myelinated fibres are visible on semithin sections. Electron microscopy reveals macrophages stripping myelin, and the presence of demyelinated and remyelinated fibres. There is also a mononuclear infiltrate.

**Treatment and prognosis:** Treatment consists of immunosuppression with prednisolone (initial dose of 2 mg/kg orally, divided q12h for 1–2 weeks, followed by gradual tapering over a period of weeks). Most cases respond favourably to this regimen, though some eventually relapse and become steroid resistant.

## Ganglioradiculitis

Ganglioradiculitis, also called sensory neuronopathy, ganglionitis and sensory polyganglioradiculoneuritis, is a rare disease in which there is non-suppurative inflammation of the dorsal root and cranial nerve sensory ganglia (Cummings *et al.*, 1983).

Clinical signs: Affected dogs are usually mature and may have an apparently sudden onset in signs that are then slowly progressive over a period of months. The signs include ataxia, hypermetria and postural reaction deficits. Spinal reflexes may be reduced, with good preservation of muscle mass and strength due to involvement of the sensory part of the spinal reflexes. Cranial nerve deficits include head tilt, dysphonia and dysphagia, facial hypalgaesia and difficulty in prehension of food. Atrophy of the muscles of mastication may occur and self-mutilation is rarely reported.

**Pathogenesis:** The aetiology of this disease is unknown but it is speculated to be immune-mediated (Porter *et al.*, 2002). There is one report of a sensory neuronopathy that could have been the result of mercury toxicity (Jeffery *et al.*, 1993). It has been reported in a variety of different breeds of dog but the Siberian Husky appears to be over-represented.

**Diagnosis:** Ante-mortem diagnosis is usually presumptive, based on compatible clinical signs and decreased sensory nerve conduction velocity. CSF findings are usually non-specific, with a mild increase in cellularity and protein levels sometimes reported. As the inflammatory infiltrate is localized to ganglia, nerve biopsy will not establish a specific diagnosis: biopsy of a dorsal root ganglion could be attempted.

**Treatment and prognosis:** There is currently no effective treatment: immunosuppression does not appear to alter the course of the disease.

#### **Polyradiculoneuritis**

Polyradiculoneuritis (inflammation of peripheral nerves and nerve roots) is probably the most common peripheral neuropathy of dogs and cats. It is likened to human Guillain—Barré syndrome.

**Clinical signs:** Signs typically start in the pelvic limbs and progress over the subsequent 2–4 days to LMN tetraparesis or tetraplegia. Spinal hyperaesthesia has been noted in some dogs.

Pathogenesis: Signs are caused by an inflammatory reaction to axons and myelin sheaths that is most intense at the level of the ventral nerve root (Cummings and Haas, 1966). Electrophysiological findings in dogs suggest that it is primarily a motor axonopathy (Cuddon, 1998). The disease can be subclassified according to cause as Coonhound paralysis (seen in North America with onset of signs 7–10 days after raccoon bites), idiopathic polyradiculoneuritis and post-vaccination polyradiculoneuritis (extremely rare). An important association in human patients is concurrent infection with a specific serotype of Campylobacter jejuni (Nachamkin et al., 1998) but no similar relationship has been established in domestic pets to date.

Diagnosis: The number of diseases that cause acute onset of LMN tetraparesis or tetraplegia is limited and polyradiculoneuritis should always be suspected when this clinical picture occurs. Other diseases to consider include botulism and, in the USA and Australia, tick paralysis. Electromyography reveals spontaneous electrical activity consistent with denervation (fibrillation potentials and positive sharp waves); nerve conduction velocities are dispersed and reduced, with nerve roots more severely affected than distal nerve (Cuddon, 1998). Definitive diagnosis is established by nerve biopsy (see Chapter 6).

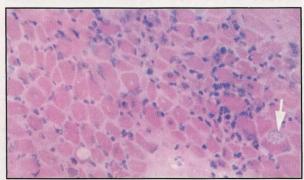
Treatment and prognosis: Treatment centres on supportive care and rehabilitation. Corticosteroid administration is not beneficial. Humans are treated by plasmapheresis and intravenous immunoglobulins but there are no reports of this in dogs or cats. The pulmonary function of recumbent animals must be monitored closely. If hypoventilation is suspected, an arterial blood gas analysis should be performed to determine whether mechanical ventilation is necessary. Animals should be turned and passive range-ofmotion exercises and massage of limbs should be performed at least four times a day. Methods of maintaining muscle mass are discussed in Chapter 24. If pulmonary function is unaffected, with adequate supportive care most animals will recover over a period of 3-6 weeks. The need for mechanical ventilation, the presence of aspiration pneumonia and severe muscle atrophy with development of contractures all worsen the outcome.

#### Protozoal neuritis

Clinical signs: Clinical signs can be extremely variable as a result of infection of muscle, peripheral nerve and the CNS. Typically the pelvic limbs are affected first and the combination of myositis and neuritis causes rigid extension of the limbs, with severe muscle atrophy and contractures developing quickly (Knowler and Wheeler, 1995). However, multifocal CNS signs can be present and can be the predominant sign (see Chapter 10).

Pathogenesis: Infection with the protozoal organisms Toxoplasma gondii and Neospora caninum can cause an intense polyradiculoneuritis in dogs, accompanied by a myositis (Greene et al., 1985; Dubey and Lindsay, 1996). Clinically significant protozoal infections affect young or immunocompromised dogs. Dogs are both definitive and intermediate hosts for N. caninum, with cattle, sheep, goats and other mammals also acting as intermediate hosts. Cats are the definitive host for *T. gondii*, with most mammals serving as intermediate hosts. Infection can occur transplacentally (common for N. caninum), by ingestion of protozoal cysts from infected secondary hosts, and by ingestion of oocysts shed in faeces (common for T. gondii). N. caninum is probably the most common protozoal infection in dogs, particularly as retrospective immunohistochemical evaluation of archived tissue confirms that many animals previously diagnosed with toxoplasmosis were actually infected with N. caninum.

*Diagnosis:* Definitive diagnosis can be made by identification of the organisms by muscle (Figure 14.26) or nerve biopsies, combined with serology. Serology alone can be confusing, with a high rate of false positive titres, particularly in the case of toxoplasmosis, and is discussed further in Chapter 10. Polymerase chain reaction (PCR) analysis of CSF may provide a more specific diagnosis in the future.



Muscle from a dog infected with *Neospora* caninum. A group of tachyzoites can be seen within a myocyte (arrowed). Original magnification X150.

**Treatment and prognosis:** Treatment of protozoal infections can be attempted using clindamycin but a combination of trimethoprim/sulphonamide and pyrimethamine may be more effective in actually killing the organisms and penetrates the CNS well. Animals

on this protocol can be supplemented with folic acid, and azithromycin can be added as it is effective in killing intracellular organisms. Prognosis depends on the severity of clinical signs and muscle contractures. Recovery of normal function is unlikely but institution of treatment can prevent progression of signs. The prognosis is better if treatment is initiated while signs are still mild, but relapses can occur.

## **Toxic diseases**

#### **Botulism**

Clinical signs: Botulism causes LMN tetraparesis that starts in the pelvic limbs as mild weakness but progresses to tetraplegia in severe cases. Cranial nerves are often involved, producing facial paresis, dysphonia, megaoesophagus and regurgitation. Autonomic signs such as mydriasis and dry eye are variably present. Onset of signs usually occurs over 2–4 days and is often preceded by a history of dietary indiscretion (usually consuming spoiled meat) and vomiting or diarrhoea. Botulism has not been reported in cats.

**Pathogenesis:** Botulism is caused by absorption of the botulinum toxin following ingestion of spoiled carrion or raw meat. The botulinum toxin, produced by *Clostridium botulinum*, is taken up at the neuromuscular junction and prevents synaptic release of acetylcholine at the neuromuscular junction. There are several forms of the botulinum toxin, but botulinum C is the only form associated with canine disease (Coleman, 1998).

*Diagnosis:* History and clinical signs are indicative of the disease. Electrophysiological studies may be supportive of the diagnosis (decreased amplitudes of compound muscle action potential, CMAP). Reduced motor nerve conduction velocity has been reported suggesting that there is a concurrent neuropathy (van Nes and van der Most van Spijk, 1986). Definitive diagnosis is difficult to establish: presence of the botulinum toxin in the serum, faeces or vomitus may be detected using a specific antitoxin to perform a neutralization test in mice, and use of an ELISA has been reported. Often the toxin is no longer detectable by the time neurological signs are evident.

Treatment and prognosis: Treatment is supportive and recovery occurs over a period of approximately 3 weeks. Affected dogs should be turned regularly, kept clean and dry, and their bladder expressed if necessary. Megaoesophagus and regurgitation should be managed by intermittent suction of the oesophagus by means of a naso-oesophageal tube, antacids (e.g. famotidine) to decrease acidity of stomach contents (decreases oesphagitis and effects of aspiration), and antibiotics for aspiration pneumonia if necessary. Ampicillin, aminoglycosides, erythromycin, ciprofloxacin and imipenem interfere with neuromuscular conduction and should be avoided. If megaoesophagus is present, the dog should

be fed while held or propped with the head up and that position maintained for approximately 30 minutes after feeding. Arterial blood gas analysis should be performed to check for hypoventilation in tetraplegic animals and in animals that may have aspirated. Passive range-of-motion exercises and massage should be performed every 6 hours while the animal is recumbent. See Chapter 24 for more details on rehabilitation.

If pulmonary function is not adversely affected, dogs have a good prognosis with adequate nursing. If aspiration pneumonia or hypoventilation develop, prognosis is grave, but recovery can occur if appropriate ventilatory support can be provided.

#### Drug-induced toxic neuropathy

These disorders are rarely encountered in clinical practice but certain drugs and substances have the potential to cause peripheral neuropathies. Examples include the chemotherapeutic drugs vincristine and cis-platinum. One case of vincristine-induced neuropathy has been reported: the dog was given 16 weekly doses of vincristine at a dose rate of 0.5 mg/m<sup>2</sup> (Hamilton et al., 1991). Signs improved following discontinuation of the drug. As radiation becomes more routine for the treatment of neoplasia, radiationinduced neuropathies will become more common. This can be a late effect and in an experimental study on intraoperative radiation in dogs paraparesis developed between 1 and 19 months after radiation if the dose exceeded 15 gray (LeCouteur et al., 1989; Johnstone et al., 1995). There are rare reports of organophosphate-induced delayed neuropathy in cats occurring with chronic exposure. Thallium toxicity, from ingestion of insecticides and rodenticides that contain this substance, has been reported in dogs and cats but the banning of this substance has made this an extremely unlikely occurrence. In Europe there was an outbreak of a generalized peripheral neuropathy in cats that was determined to be the result of contamination of their food with the ionophore salinomycin (van der Linde-Sipman et al., 1999). The cats developed tetraplegia and many died or were euthanased. Similar signs have been reported in dogs that ingested food contaminated with lasalocid (Safran et al., 1993). Contamination of food in both these instances occurred at the processing plant, as ionophores are frequently added to ruminant or porcine feed as a growth promoter.

#### Tick paralysis

Certain species of female ticks contain a toxin within their saliva that causes presynaptic blockade of acetylcholine release and a flaccid tetraplegia (Malik and Farrow, 1991). Signs appear after the tick has been attached for 3–5 days and progress over 1–3 days. They usually resolve within an equal period following removal of the tick, except in the case of the Australian tick, in which signs can progress following tick removal. This disease is not a problem in the UK as the tick species involved are not present in this country. It is encountered commonly in the USA and more severe forms occur in Australia and Africa.

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# **Paraparesis**

Joan R. Coates

## Introduction

*Paraparesis* is a non-specific term for bilateral motor dysfunction of the pelvic limbs.

Paraparesis is a very common presentation in small animal veterinary practice and can be caused by orthopaedic, muscle, neuromuscular junction, nerve and spinal cord dysfunction. More rarely, systemic and metabolic disorders can present as episodic or progressive paraparesis (e.g. cardiac and pulmonary dysfunction, endocrine and electrolyte disturbances) and animals with drug-induced side-effects (e.g. phenobarbital and potassium bromide) may show pelvic limb dysfunction manifested as ataxia. Diseases of the thoracolumbar spinal cord are the most common cause of paraparesis and, as late or misdiagnosis of many of these disorders can have catastrophic consequences for the patient, it is important to fully understand how to evaluate and manage paraparetic animals.

## **Clinical signs**

Paraparesis, by definition, represents motor deficits in the pelvic limbs. Abnormal gait descriptions include:

- Ataxia loss of proprioception; incoordination
- Fatigability applies when one or more muscles become weaker with repetitive but normal use and may imply neuromuscular dysfunction
- Paresis reduced voluntary motor function
- Paralysis or paraplegia absence of voluntary motor function
- Weakness a non-specific term referring to an inability to carry out a desired movement with normal force because of a reduction in strength of the muscles necessary to carry out the movement.

Paraparesis may be accompanied by changes in muscle tone that are elicited by passive movements including flaccidity, spasticity and rigidity.

- Flaccidity the absence of normal muscle tone.
- Spasticity (in quadripeds) a selective increase in extensor tone.
- Rigidity an increase of flexor and extensor tone.

Schiff–Sherrington posture is characterized by thoracic limb extension with normal to sometimes decreased tone in the pelvic limbs (Figure 15.1). A lesion to the thoracolumbar spinal cord segments alters the ascending inhibitory pathways from the border cells in the lumbar grey matter (L2–L4). Axons from these cells cross to ascend in the contralateral fasciculus proprius to terminate in the cervical intumescence. Loss of this ascending inhibition to the thoracic limbs results in extension. In spite of this increase in extensor tone the thoracic limbs are normal neurologically with respect to motor function and proprioception. Schiff–Sherrington posture does not indicate that the spinal cord lesion is irreversible.



An example of a Schiff–Sherrington posture with increased extensor tone in the thoracic limbs and paralysis in the pelvic limbs. In addition, a demonstration of absent deep pain perception is an important prognostic indicator.

Clinical signs of thoracolumbar spinal cord disorders reflect sensory, motor and autonomic dysfunctions of the pelvic limbs, tail, bladder and gastrointestinal tract (Figure 15.2). Depending upon the severity of pelvic limb dysfunction, the paresis may or may not be clinically obvious.

#### Gait

Gait should be evaluated at a slow and fast pace and when walking up and down steps.

#### Ataxic gait

Animals with spinal cord disease have an ataxic gait and postural reaction deficits (specifically conscious proprioception deficits). Conscious proprioception is a

## Chapter 15 Paraparesis

Evaluation	Spinal cord segments T3-L3	Spinal cord segments L4–S3
Mental status	Normal	Normal
Posture	Normal or pelvic limbs tucked under body and altered tail carriage	Normal or pelvic limbs tucked under body and altered tail carriage
Gait	Pelvic limb ataxia; symmetrical or asymmetrical paraparesis/plegia	Pelvic limb ataxia, symmetrical or asymmetrical (more often with cauda equina) paraparesis and/or plegia
Cranial nerves	Normal	Normal
Postural reactions	Mild to severe deficit or absent	Mild to severe deficit or absent
Spinal reflexes	Normal to hyperreflexic pelvic limb(s)	Hyporeflexia or areflexia; pseudo-hyperreflexic patellar reflex with sciatic nerve dysfunction
Spinal hyperaesthesia	Variable; dependent on disease process	Variable; dependent on disease process
Pain perception	Variable; dependent on disease severity	Variable; dependent on disease severity
Micturition	Usually affected with loss of motor function, detrusor areflexia–sphincter hypertonia	None or mild to severe detrusor areflexia; sphincter hypotonia

15.2 Clinical signs of thoracolumbar and lumbosacral spinal cord dysfunction.

non-weight-bearing test used to discriminate between orthopaedic and neurological lameness. Subtle proprioceptive loss and paresis may become more apparent during postural reaction testing (i.e. hopping, extensor postural thrust and wheel-barrow reaction).

- Spinal reflexes, myotatic and withdrawal (flexor) reflex can assist further with neuroanatomical localization (see Chapter 1).
- The cutaneous trunci reflex can assist with localization of a thoracolumbar lesion but is not always a reliable indicator.
- Assessment of pelvic limb pain perception (see Chapter 1) is extremely important in paraplegic animals as it provides critical prognostic

information (see also Chapter 19).

 Asymmetry of neurological deficits is common with vascular, inflammatory and compressive myelopathies.

Presence of paraspinal hyperaesthesia also assists with the differential diagnoses (Figure 15.3). Paraspinal hyperaesthesia usually indicates a compressive and/or an inflammatory cause. Pain sensitive structures include the periosteum of the vertebrae, meninges, nerve roots and intervertebral disc (see Chapter 13). Disorders that classically do not manifest paraspinal hyperaesthesia are degenerative spinal cord diseases, intramedullary neoplasia and fibrocartilaginous embolic (FCE) myelopathy.

Diseases exhibiting no paraspinal hyperaesthesia	Onset
Degenerative  Degenerative myelopathies; spinal muscular atrophies; central axonopathies; hereditary ataxia in Smooth Fox and Jack Rus Terriers; leucoencephalomyelopathy of Rottweilers; neuroaxonal dystrophies; nervous system degeneration in Ibizan Hounds; Afghan Hound myelopathy; hypomyelinogenesis; dysmyelinogenesis; storage diseases; spondylosis deformans; dural ossification	Ssell Chronic
Anomalous Myelodysplasia	Chronic
Neoplasia Primary: Intramedullary (ependymoma, glioma)	Chronic; may have acute manifestation
Inflammatory Infectious myelitis (viral, protozoal)	Usually acute
Vascular Fibrocartilaginous embolic (FCE) myelopathy; thrombosis; infarction	Acute
Diseases exhibiting paraspinal hyperaesthesia	
Degenerative Calcinosis circumscripta; intervertebral disc disease; spinal extrasynovial cyst; mucopolysaccharidosis	Acute or chronic
Anomalous Vertebral malformations; spina bifida; syringohydromyelia	Chronic

Disorders of the thoracolumbar spinal region by onset and pain status. (continues)

15.3

Metabolic Hyperchylomicronaemia	Chronic
Neoplastic Primary: Extradural (vertebral, lymphoreticular); Intradural-extramedullary (nerve sheath tumour, meningioma, nephroblastoma) Secondary: Metastatic (mammary carcinoma, haemangiosarcoma)	Acute or chronic
ldiopathic Diffuse idiopathic skeletal hyperostosis	Usually chronic
Inflammatory Infectious: Meningitis/myelitis (viral, fungal, bacterial, protozoal, rickettsial, algal, spinal empyema); discospondylitis (bacterial, fungal); vertebral physitis Non-infectious: Granulomatous meningoencephalomyelitis; steroid-responsive meningitis; vasculitis	Usually acute
Trauma Traumatic disc herniation; vertebral fractures/luxations	Acute

15.3

(continued) Disorders of the thoracolumbar spinal region by onset and pain status.

#### Stiff gait

A stiff or stilted gait is characteristic for an animal with orthopaedic, muscle or neuromuscular junction disease. In order to differentiate orthopaedic from neurological disease, the animal will often be required to undergo strenuous exercise. In cases of neurological disease this will exacerbate the paraparesis; whereas, clinical signs often improve with exercise in animals with orthopaedic disease. In addition, the following should be noted to help differentiate the origin of the gait deficit:

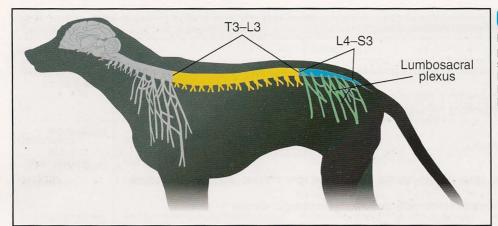
- Animals with orthopaedic disease will not have conscious proprioceptive deficits, although the associated loss of strength with these conditions may make interpretation of these tests difficult
- Myopathic disease usually presents with generalized weakness and exercise intolerance that can be episodic or persistent. Gait is usually stiff and stilted or 'bunny-hopping'. Exercise intolerance and episodic weakness are often not obvious until the animal is exercised. Commonly in myopathic disease, the pelvic limbs are affected first and more severely than the thoracic limbs, and may therefore initially present as paraparesis (see Chapter 17 for further details on these disorders and tetraparesis). Muscle palpation may reveal severe atrophy or hypertrophy with or without tremors and/or fasciculations. In addition, myopathies (and polyneuropathies) can result in dysphagia, dyspnoea and dysphonia. Depending upon the severity of atrophy the range of joint movement may be limited. Pain may also be evident upon palpation of the muscles
- The neuromuscular junction disorder that is most often confused with other paraparetic disorders is generalized myasthenia gravis (MG). Although rare, MG may manifest as an episodic weakness with pelvic limb involvement only. The gait of affected animals can show a shortened stride or 'bunny-hop' that progresses to collapse. Strength returns with rest (see Chapter 17).

Neuropathies are characterized by flaccid paresis, postural reaction deficits and neurogenic muscle atrophy. Paraesthesia or analgesia may be evident with involvement of the sensory component of the nerve. Gait evaluation commonly reveals moderate to severe ataxia. Distal limbs may have a flaccid appearance. Muscle palpation reveals severe atrophy and in chronic cases, joint contracture. Muscle fasciculations may be present. Spinal reflexes often are decreased or absent. Neuropathies can be responsible for dysphagia, dysphonia and dyspnoea.

#### **Lesion localization**

Thorough physical, orthopaedic and neurological examinations of the patient are crucial for localizing the clinical signs and avoiding unnecessary diagnostic testing and client expense. A patient with suspected orthopaedic disease should have a neurological examination.

Neuroanatomical localization of paraparesis is specified to the spinal cord segments T3-L3 or L4-S3 (Figure 15.4) based upon signs of upper motor neuron (UMN) or lower motor neuron (LMN) limb weakness, respectively (see Chapters 1 and 2). UMN weakness refers to a lesion that interrupts the descending motor pathways from supraspinal neurons that converge on the LMN pool. Clinical signs of UMN weakness manifest as paresis and/or plegia with normal to increased spinal reflexes (hyperreflexia) and muscular hypertonia. LMN weakness refers to a lesion of the ventral spinal cord grey matter and its axon coursing to the muscle through the spinal nerve roots and peripheral nerve. LMN weakness clinically manifests as paresis and/or plegia, decreased to absent spinal reflexes (hyporeflexia to areflexia), decreased muscle tone (flaccidity) and muscle atrophy that is severe and rapid in onset. The sacral and coccygeal regions are localized according to LMN signs involving the perineal region, bladder function, urethral tone and tail tone (see Chapter 18).



## 15.4

Lesion localization for paraparesis; spinal cord segments T3–L3 and L4–S3, and the lumbosacral plexus are highlighted.

A stiff or stilted gait, muscle atrophy and lack of proprioceptive deficits are suggestive of orthopaedic, junctional or myopathic disease. LMN signs relevant to the pelvic limbs, with a lack of involvement of the tail and bladder, lead to the suspicion of a peripheral neuropathy rather than a process affecting the spinal cord or cauda equina. Neuropathies may be associated with signs of megaoesophagus.

Due to the multiplicity of anatomical dysfunctions that can produce clinically similar disorders, the clinician faces a diagnostic dilemma. Aged patients often have concurrent orthopaedic and neurological disorders, which further complicate the examination process. For example, in middle-aged, large-breed dogs, disorders that often mimic each other and coexist include:

- Degenerative lumbosacral stenosis
- · Degenerative myelopathy
- Type II intervertebral disc disease
- Degenerative joint disease as a result of hip dysplasia or rupture of the anterior cruciate ligament.

To further complicate matters a specific ante-mortem diagnostic test is lacking for some diseases. For example, in German Shepherd Dogs the diagnosis of degenerative myelopathy should always be a consideration for paraparesis, even in the face of other causes. It is important to note that signs of pelvic limb dysfunction can present prior to signs of thoracic limb paresis in some cases of cervical spinal cord disease (e.g. giant breed wobbler syndrome) and in generalized peripheral neuropathies, junctionopathies and myopathies. These disorders are considered in more detail in Chapters 14 and 17.

It is important to remember that localization refers to spinal cord segments rather than vertebrae. Thus, a lesion that localized to the L4–S3 spinal cord segments could lie anywhere caudal to the second lumbar vertebra (the approximate site of the L4 spinal cord segment) (see Chapter 2).

# **Pathophysiology**

The severity of the motor and sensory deficits from spinal cord disease is dependent upon the rapidity of disease onset, extent of spinal cord involvement and the area within the vertebral column that is affected. Spinal cord dysfunction can be a secondary consequence of extrinsic or intrinsic injuries to the spinal column. Traumatic aetiologies, such as vertebral fractures, luxation and penetrating injuries from missiles or animal bites, are examples of extrinsic injuries. Intrinsic injuries include embolization of the spinal cord vasculature, extrusion of the nucleus pulposus and developmental anomalies. As for tetraparesis (see Chapter 14) disease processes affecting the spinal cord and peripheral nerves and muscles may be compressive, concussive, inflammatory, vascular, metabolic or degenerative.

Animals with acute, severe thoracolumbar spinal cord injuries may develop an unusual systemic complication known as neurogenic shock.

Neurogenic shock is associated with cervical or cranial thoracic injury to the spinal column. This has been observed in people and experimentally in dogs and cats but is rarely evident in clinical patients.

This syndrome results from sympathetic loss (decreased blood pressure and heart rate resulting from unopposed vagal tone) and continual vagal tone. This phenomenon results in a loss of spinal cord blood flow regulation and subsequent ischaemia. Neurogenic shock resolves with fluid therapy and pressor agents.

## **Neurodiagnostic investigation**

History and findings of physical and neurological examinations will identify a neurological problem and assist with neuroanatomical localization and consideration of differentials. The onset (acute or insidious), rate of progression (rapid or gradual) and temporal relation (intermittent and/or episodic, stable or chronic) can be established. A recommended diagnostic approach to spinal cord diseases is as follows:

- Complete blood count (CBC), serum biochemistry profile and urinalysis
- Thoracic radiographs in animals >5 years of age, and after trauma
- Survey spinal radiographs can assist with recognition of obvious abnormalities such as discospondylitis, luxations and bone neoplasia. If an abnormality is not seen, advanced imaging

- and cerebrospinal fluid (CSF) analysis are indicated
- CSF collection preferably from the cerebellomedullary cistern and caudal lumbar region
- Myelography and epidurography are useful for the detection and characterization of compressive spinal cord lesions (extradural, intradural and intramedullary) and for determining the extent of the compression (Figure 15.5).



Lateral myelographic view of the cranial lumbar spine demonstrating extradural compression secondary to discospondylitis.

- Computed tomography (CT) is used as a primary method to evaluate the spine or assist with determining lesion extent after myelography
- Magnetic resonance imaging (MRI) is becoming a more common diagnostic technique as it is particularly useful in the detection of lesions within the spinal cord.

Additional diagnostic procedures include electrodiagnostic evaluation (electromyography and nerve conduction studies), nerve and muscle biopsy, CSF protein electrophoresis, serology and exploratory surgery.

## **Differential diagnosis**

The anatomical localization and distinguishing features of lesions that cause paraparesis are summarized in Figure 15.6.

# **Diseases that cause paraparesis**

The causes of paraparesis are summarized in Figure 15.7.

Location	Distinguishing factors on examination  Paraparesis, postural reaction and CP deficits (pelvic limbs); intact to increased spinal reflexes; ± focal spinal hyperaesthesi	
T3–L3		
L4-S3	Paraparesis, postural reaction and CP deficits (pelvic limbs); decreased to absent spinal reflexes; ± change in tail carriage and/or tone; ± incontinence; ± focal spinal hyperaesthesia	
Bilateral orthopaedic disease of pelvic limbs	Paraparesis but stilted gait; normal CPs; abnormal findings on orthopaedic examination	
C1-T2	As for T3–L3 plus subtle postural reaction or gait deficits in thoracic limbs; neck pain.	
Peripheral neuropathy	As for L4–S3 but no change in tail function or continence; ± laryngeal paralysis; ± megaoesophagus; ± thoracic limb involvement	
Junctional disease	Normal CP; spinal reflexes may be initially normal but decrease with repetition; often see paraparesis $\pm$ thoracic limb involvement that is exacerbated by exercise or activity; no evidence of spinal pain $\pm$ laryngeal paralysis; $\pm$ megaoesophagus; no evidence of incontinence	

15.6 Anatomical localization of lesions that can cause paraparesis. CP = conscious proprioception.

Mechanism of disease	Specific diseases	
Degenerative	Calcinosis circumscripta [14] Degenerative myelopathy [15] Dural ossification [15] Intervertebral disc disease (Hansen types I and II) Mucopolysaccharidosis [15] Spinal synovial cyst [14, 15] Spondylosis deformans [13]	[14, 15]
Anomalous	Dermoid sinus [14, 15] Osteochondromatosis [15] Vertebral and spinal cord anomalies [5, 13, 15] Syringohydromyelia [13, 14]	
Metabolic	Diabetes mellitus (neuropathy) [14]	

Causes of thoracolumbar spinal cord and peripheral nerve disease. Numbers in square brackets denote chapters where details are given. (continues)

Mechanism of disease	Specific diseases  Extradural: metastasis; vertebral tumours (sarcomas, plasma cell tumours); lymphoma [15] Intradural-extramedullary: meningiomas; nerve sheath tumours; spinal neuroepithelioma (nephroblastoma); metastasis [15] Intramedullary: ependymomas; gliomas; metastasis; round cell tumours [15] Insulinoma (paraneoplastic neuropathy) [14]	
Neoplastic		
Nutritional	Hypervitaminosis A [13]	e le dell'echer end characterization oi
Inflammatory	Discospondylitis/osteomyelitis/physitis [13] Granulomatous meningoencephalomyelitis [10] Infectious meningoencephalomyelitis [10, 15] Spinal empyema [14] Steroid-responsive meningitis–arteritis [13] Vertebral physitis [15]	entradulation (premodulary) and localities the thing the compression (References 15,5).
Idiopathic	Arachnoid cysts [14] Diffuse idiopathic skeletal hyperostosis [15]	
Traumatic	Fracture/luxation [14, 15, 19] Spinal cord contusion [14, 19] Traumatic disc herniation [14]	
Toxic	Antiepileptic drugs [7, 15]	
Vascular	Fibrocartilaginous embolism [14, 15] Spinal cord/epidural haemorrhage [14] Thromboembolic disease [15]	

15.7

(continued) Causes of thoracolumbar spinal cord and peripheral nerve disease. Numbers in square brackets denote chapters where details are given.

## Degenerative diseases

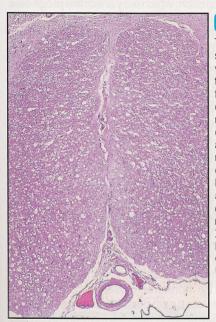
## Degenerative myelopathy

Clinical signs: Dogs with degenerative myelopathy (DM) show an insidious, progressive ataxia and paresis of the pelvic limbs ultimately leading to paraplegia and euthanasia (Averill, 1973). If pelvic limb hyporeflexia is observed, reflecting nerve root involvement, the disease is termed canine degenerative radiculomyelopathy (CDRM) (Griffiths and Duncan, 1975). Although the German Shepherd Dog is the most commonly affected breed, DM has been reported in other breeds and is emerging in a number of purebred dogs, such as the Pembrokeshire Welsh Corgi. Age of onset of neurological signs is usually 5 years or older with a mean age of 9 years; however, young dogs can be affected (Longhofer et al., 1990).

Neuroanatomical localization is characterized by UMN signs to the pelvic limbs implying a spinal cord lesion between T3 and L3. DM can progress to paraplegia over 6-12 months after the suspected diagnosis. Pelvic limb tremors or muscle fasciculations are sometimes observed during stance and gait. Gait abnormalities progress from truncal ataxia to severe paraparesis, characterized by spasticity and long strides, typical of an UMN disease gait. Proprioceptive loss is recognized by toe dragging, knuckling deficits and ataxia, and pelvic limb dysfunction is usually asymmetrical. Thoracic limb function is usually spared except during end-stage disease. Spinal reflexes are usually present or exaggerated. Presence of a crossed extensor reflex is variable during flexor withdrawal evaluation. Decreased or absent patellar reflexes may indicate concurrent, or progression to, LMN involvement. Disuse atrophy of pelvic limb musculature develops gradually as paresis progresses. Control of urination and defecation may be affected late in the disease process. Lack of paraspinal hyperaesthesia is a key clinical feature of degenerative myelopathy. Nociception is usually unaffected.

Pathogenesis: The aetiology of degenerative myelopathy remains unknown. Griffiths and Duncan (1975) hypothesized DM to be a 'dying-back disease' confined to the central nervous system (CNS), suggesting a toxic aetiology. Braund and Vandevelde (1978) refuted that hypothesis based upon morphometric data and instead suggested an inherited genetic cause. However, the late onset of the disease makes it difficult to collect data from parents and siblings to substantiate this theory. Recently, studies of the brain of DM affected dogs showed neuronal degeneration and loss in the red nucleus, lateral vestibular nucleus and in the dendate nucleus (Johnston et al., 2000). An immunological role was proposed based upon observations of depressed responses to thymus-dependent mitogens (Waxman et al., 1980b) and increased concentrations of circulating immune complexes (Waxman et al., 1980a). A more recent study showed immunohistochemical evidence for immunoglobulin and complement deposition in the spinal cord of DM dogs (Barclay and Haines, 1994). Although immune-related degenerative disease is a plausible theory, immunosuppressive therapies have shown no long-term benefits in halting the progression of DM (Clemmons, 1989). Decreased serum levels of vitamin E and B12 have also been proposed as causes of this disease but largely refuted by recent studies (Johnston et al., 2000; Fechner et al., 2003).

Diagnosis: Tentative antemortem diagnosis is presently based upon ruling-out other diseases causing progressive myelopathy (Kneller et al., 1975). Common differentials include intervertebral disc disease, inflammatory disease and spinal cord neoplasia. Hip dysplasia and degenerative lumbosacral stenosis (LSS) often can be confused with the diagnosis of DM although the neurological findings are different if a careful examination is performed. It is not uncommon for DM affected dogs to have coexisting neurological and orthopaedic diseases. Neurodiagnostic techniques for evaluation of spinal cord disease include CSF analysis, electrodiagnostic testing, myelography, CT and MRI. Definitive diagnosis of DM is determined postmortem by histopathological examination of the spinal cord (Figure 15.8). Neuropathological lesions involve the spinal cord myelin and axons in all funiculi (Averill, 1973; Griffiths and Duncan, 1975) but most extensively in the midthoracic region and are described as discontinuous, bilateral and asymmetrical (Braund and Vandevelde, 1978).



## 15.8

Transverse section of the ventral funiculi of the spinal cord from a dog with degenerative myelopathy demonstrating axonal and mvelin degeneration. Haematoxylin and eosin stain, original magnification X40. (Courtesy of Dr P. March, Ohio State University)

Treatment and prognosis: Until a cause of DM is known it is difficult to recommend an appropriate treatment regimen. Aminocaproic acid, an antiprotease agent, has been advocated for long-term management of DM (Clemmons, 1992); however, there have been no published clinical data to support drug efficacy. While treatment of vitamin deficiencies can resolve neurological disease in some animals, therapy with parenteral cyanocobalamin or oral alpha-tocopherol did not affect neurological progression in a study of DM affected dogs (Johnston et al., 2000, 2001; Williams, unpublished data). Combination therapies with an exercise regimen have also been advocated for treatment of DM (Clemmons, 1991).

Long-term prognosis is considered poor. Dogs often lose the ability to ambulate the pelvic limbs within 4–6 months of diagnosis. The disease will eventually progress to affect the thoracic limbs.

#### **Dural ossification**

Dural ossification is also known as osseous metaplasia. Dural ossification is a benign condition of bony plaques on the inner surface of the dura mater, common in the cervical and lumbar regions of small and large breed dogs >2 years of age (Morgan, 1969). These are identified as radiopaque lines that outline the spinal cord and are best visualized at the intervertebral foramina. Dural ossification is rarely associated with clinical disease.

## Type I intervertebral disc disease

Clinical signs: Onset of neurological signs may be peracute (<1 hour), acute (<24 hours) or gradual (>24 hours). Dogs presented with peracute or acute thoracolumbar disc extrusions may manifest clinical signs of spinal shock or Schiff–Sherrington postures. These indicate acute and severe spinal cord injury but do not determine prognosis. The degree of neurological dysfunction is variable and affects prognosis. Clinical signs vary from spinal hyperaesthesia only to paraplegia with or without pain perception. Dogs with back pain only are usually reluctant to walk and may show kyphosis. Dogs with back pain alone and no neurological deficits often have myelographic evidence of substantial spinal cord compression.

Neuroanatomical localization for thoracolumbar lesions is determined by intact (T3–L3) or hyporeflexive (L4–S3) spinal reflexes and by the site of paraspinal hyperaesthesia. Asymmetrical neurological deficits may be less reliable for determining the site of disc extrusion.

Pathogenesis: Hansen (1951) first classified intervertebral disc disease (IVDD) as type I and type II. Hansen type I IVDD is herniation of the nucleus pulposus through the annular fibres and extrusion of nuclear material into the spinal canal. Hansen type I IVDD is typically associated with chondroid disc degeneration. The disc extrudes through the dorsal annulus causing ventral, ventrolateral or circumferential compression of the spinal cord.

- Acute disc extrusion is characterized by the presence of soft disc material within the vertebral canal and extradural haemorrhage.
- Chronic disc extrusion is characterized by extradural fibrous adhesions around the herniated disc material, which has often become a hard mineralized mass.

Hansen type I IVDD typically affects chondrodystrophoid dogs and has an acute onset. However, large non-chondrodystrophoid breeds of dog such as the Doberman Pinscher and Labrador Retriever, may also be affected (Cudia and Duval, 1997).

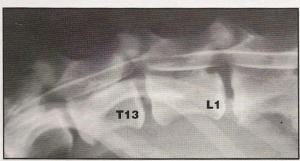
Hoerlein (1952) determined that IVDD accounted for 2.02% of all diseases diagnosed in dogs. Incidence of IVDD peaks at 4–6 years of age in chondrodystrophoid breeds and at 6–8 years in non-chondrodystrophoid breeds (Priester, 1976). The Dachshund had the highest incidence of frequency followed in succession by the Pekingese, Welsh Corgi, Beagle, Lhasa Apso and Miniature Poodle (Hoerlein, 1987).

Hansen type I IVDD most commonly occurs within the thoracolumbar region of chondrodystrophoid breeds. The thoracolumbar junction (T12–T13 to L1–L2) accounted for the highest incidence of all disc lesions (Gage, 1975; Hoerlein, 1987). The incidence of thoracolumbar IVDD progressively decreases from T12–T13 caudally. The most common site for Hansen type I IVDD in large, non-chondrodystrophoid breeds is the interspace between L1 and L2 (Cudia and Duval, 1997).

*Diagnosis:* The initial diagnosis of thoracolumbar IVDD is obtained from the signalment, history and neurological examination. Differential diagnoses to be considered include trauma, FCE, discospondylitis, neoplasia and (meningo) myelitis. Diagnosis of thoracolumbar disc extrusion and/or protrusion is confirmed by radiography and surgery.

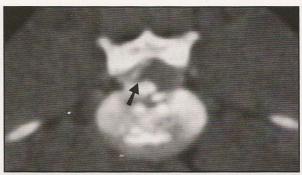
Survey spinal radiography can help to determine the diagnosis and site of a thoracolumbar disc extrusion if radiographic signs are well defined and consistent with neuroanatomical localization (see Chapter 5). Studies of dogs with surgically confirmed thoracolumbar IVDD showed that when identifying the site of disc extrusion survey radiography had an accuracy of 68–72%; but the percentage accuracy was higher with myelography (Kirberger *et al.*, 1992; Olby *et al.*, 1994). Normal variants for the thoracolumbar spinal region include narrowing of the anticlinal disc space at T10–T11 and of the L4–L6 interspaces (Widmer, 1998).

As survey radiographs identify the correct site of disc extrusion in only about 70% of cases, further imaging, such as myelography, is strongly recommended by most neurosurgeons prior to surgery. Myelographic contrast injection at the caudal lumbar region is preferred over the cerebellomedullary cistern for demonstrating thoracolumbar disc extrusion (see Chapter 5) (Kirberger and Wrigley, 1993; Lamb, 1994). Longitudinal lesion localization by myelography for thoracolumbar IVDD (Figure 15.9) varies in accuracy from 40% to 97%, but is usually close to 90% (Black, 1988; Kirberger and Wrigley, 1993; Olby *et al.*, 1994).



Lateral myelographic view of an extradural compression on the ventral aspect of the spinal cord at the T13–L1 intervertebral disc interspace suggestive of an intervertebral disc extrusion.

CT or MRI are used alone or as an adjunct to myelography to more completely delineate lateralization of extruded disc material (Figure 15.10). CT has been shown to be more accurate than myelography at identifying the major site of disc herniation and has the advantage of being a more rapid test with fewer



Transverse CT image of a lateral disc extrusion at the T12–T13 intervertebral disc interspace (arrowed).

side-effects than myelography (Olby et al., 1999). MRI can provide multiplanar views of the cord compression allowing an accurate surgical approach and can help to identify associated vertebral canal haemorrhage and determining the extent of surgical decompression required. MRI can also identify parenchymal lesions, such as oedema or infarction, which may affect the prognosis.

#### Treatment:

Conservative management: Indications for non-surgical treatment of thoracolumbar IVDD include a first-time incident of spinal pain only, mild to moderate paraparesis and the financial constraints of the client. The last is the only reason for non-surgical treatment of a recumbent patient, which should always be considered a surgical candidate if possible. Dogs can be managed with strict cage rest for 4-6 weeks combined with pain relief using anti-inflammatory drugs, opioids and muscle relaxants. Gastrointestinal protectants also may be necessary with use of anti-inflammatory therapies. Never use non-steroidal anti-inflammatory drugs (NSAIDs) in combination with corticosteroids as gastric ulcers can result and in some cases these may lead to the death of the animal. Acupuncture also has been advocated as a treatment for pain management.

Dogs should be monitored closely for deterioration of neurological status. If pain persists or the neurological status worsens, surgical management is recommended. Success rates for conservative management of ambulatory dogs with pain only or mild paresis ranges from 82% to 100% (Funkquist, 1978; Davies and Sharp, 1983). Studies have shown that recovery rates in nonambulatory dogs are lower and recurrence rates higher following conservative rather than surgical treatment. Methylprednisolone sodium succinate has been advocated as an adjunctive treatment of acute disc herniations causing paraplegia (see Chapter 19).

Surgical management: Indications for surgical management of thoracolumbar IVDD include spinal pain or paresis unresponsive to medical therapy, recurrence or progression of clinical signs, paraplegia with intact deep pain perception and paraplegia without deep pain perception for <24–48 hours. Prolonged loss of deep pain perception (>48 hours) carries a poor prognosis and owners should be made aware of this prior to surgery. However, it is often difficult to know when deep pain perception was lost; in addition recovery has

been observed in dogs that had surgery more than 5 days after the onset of paraplegia. Surgery includes spinal cord decompression by removal of extruded disc material. Chronicity of disc extrusion at the time of surgery may influence the ease with which extruded disc material can be removed.

Decompressive procedures for thoracolumbar IVDD include dorsal laminectomy (Funkquist, 1970; Prata, 1981), hemilaminectomy (Hoerlein, 1956) and pediculectomy (also termed mini-hemilaminectomy) (Braund, 1976; Bitetto and Thacher, 1987). These approaches are described in Chapter 21. There are advantages and disadvantages of each decompressive technique. Hemilaminectomy significantly improves retrieval of extruded disc material with minimal spinal cord manipulation; a clear advantage over pediculectomy and dorsal laminectomy. Pediculectomy is the least invasive and least destabilizing technique but these advantages may not be clinically significant except in cases that require a bilateral approach to the vertebral canal. Unilateral facetectomy and fenestration do not significantly destabilize the spine in lateral bending, which suggests that the articular facets of the thoracolumbar spine are more important to stiffness in axial rotation and extension (Schulz et al., 1996).

The type of decompressive procedure may not affect outcome; however, the ability to retrieve disc material depends on the decompressive procedure. The primary purpose of decompressive surgery is to provide adequate exposure to allow removal of disc material while minimizing spinal cord manipulation. Hemilaminectomy allows easier access to extruded disc material and the dorsolateral approach allows access to the disc spaces for fenestration. McKee (1992) reported retrieval of disc material in 93% of dogs that had hemilaminectomy compared with 40% of dogs that had dorsal laminectomy, although initial neurological recovery after hemilaminectomy was not significantly different when compared with that following dorsal laminectomy. Radical dorsal laminectomy

15.11

(removal of pedicle—Funkquist A) has an increased risk of constrictive laminectomy membrane formation (Gage and Hoerlein, 1968).

Durotomy: This is ineffective as a treatment for acute compressive spinal cord trauma unless performed within 2 hours of the trauma occurring (Parker, 1975). Durotomy allows visualization of the spinal cord parenchyma to determine the extent of swelling and the presence of myelomalacia. Absence of visual evidence of myelomalacia does not guarantee functional recovery; conversely, functional recovery may still occur despite presence of focal myelomalacia.

Fenestration: First described by Olsson (1951) fenestration has been advocated as a treatment and prophylactic procedure for disc disease. Surgical approaches for disc fenestration include dorsolateral, lateral and ventral incisions. The effectiveness of fenestration is related to the amount of nucleus pulposus removed (Shores *et al.*, 1985). Multiple disc fenestration is commonly performed at T11–T12 through L3–L4; however, the more commonly affected disc interspaces for extrusion are T12–T13 to L2–L3.

**Prognosis:** Overall success rates after decompressive surgery range from 58.8% (Brown *et al.*, 1977) to 95% (Schulman and Lippincott, 1987). However, the success of a surgical approach may depend on what criteria are used to define it, how long after the surgery the patient is assessed, as well as the outcome which the owners are willing to accept. Surgical success may be improvement of the patient's pre-surgery neurological grade but may not mean that the patient is functionally normal, and residual signs, e.g. incontinence, can be unacceptable to many owners.

Differences in recovery rates of non-ambulatory dogs vary according to the severity of neurological dysfunction (neurological grade), time interval from initial clinical signs to surgery and speed of onset of signs (Figure 15.11).

Neurological status and complications	Conservative treatment (without surgery)	Surgical treatment		
Pain only	75-85% (Funkquist, 1978; Hoerlein, 1987;	96% (Sukhiani <i>et al.</i> , 1996)		
Ataxia/paraparesis	Davies and Sharp, 1983)	65–83% (Brown et al., 1977); 96% (Schulman and Lippincott, 1987)		
Paraplegia with superficial pain	51% (Funkquist, 1970)	81% (Funkquist, 1970); 42% (Brown <i>et al.</i> , 1977); 79% (Schulman and Lippincott, 1987)		
Paraplegia with deep pain	50% (Davies and Sharp, 1983)	89% (Gambardella, 1980); 86% (Ferreira <i>et al.</i> , 2002)		
Deep pain negative 7% (Davies and Sharp, 1983)		7% (Henry, 1975); 47% (Brown <i>et al.</i> , 1977); 50% (Gambardella, 1980); 76% (Anderson <i>et al.</i> , 1991); 62% (Scott and McKee, 1999) 58% (Olby <i>et al.</i> , 2003)		
Ascending myelomalacia		3–6% (Denny, 1978; Davies and Sharp, 1983); 9% (Scott and McKee, 1999) 11% (Olby <i>et al.</i> , 2003)		
Recurrence	34% (Davies and Sharp, 1983); 40% (Levine, 1984); 33% (Ferreira <i>et al.</i> , 2002)	27% (Levine, 1984); 23% (Black, 1988); 13% (Scott, 1997); 5%ª (Muir, 1995); 4%ª (McKee, 1992);16%ª (Levine, 1984); 14%ª (Ferreira <i>et al.</i> , 2002); 6%ª (Olby <i>et al.</i> , 2003)		

Success rates for medical *versus* surgical treatment in dogs with thoracolumbar intervertebral disc disease. 
<sup>a</sup> Hemilaminectomy with fenestration.

Neurological grade: Deep pain perception is considered the most important prognostic indicator for a functional recovery. In general the majority of dogs with intact deep pain perception, whether paraplegic or simply paraparetic, have an excellent prognosis particularly if treated surgically. Dogs with loss of deep pain perception for more than 24-48 hours prior to surgery have a poorer prognosis for return of function. Without surgery, or with delayed surgery, dogs with absence of deep pain perception have an extremely guarded prognosis, although duration of absence of deep pain perception prior to surgery as a prognostic indicator is controversial. Recovery rates for dogs with thoracolumbar IVDD and absent deep pain perception range from 0-76%. A recent study of 87 dogs with loss of deep pain perception reported 58% of the animals regained deep pain perception and the ability to walk (Olby et al., 2003). In summary, dogs with absence of deep pain perception that have surgery within 12-36 hours have a better chance of more rapid and complete recovery than those with delayed surgery.

Dogs with more severe neurological dysfunction have a longer period of recovery (Brown et al., 1977). The mean time from post-surgery to walking varied from 10 days for pain only or paraparetic dogs to 51.5 days for paraplegic dogs (Brown et al., 1977). More recent long-term studies reported recovery times of 2–14 days for dogs that were either ambulatory or non-ambulatory with voluntary motor movement, and up to 4 weeks for paraplegic dogs (Yovich et al., 1994; Scott, 1997).

Onset and duration of clinical signs: There are many contradictory studies about the effect of (a) the speed of clinical sign onset and (b) the duration of the clinical signs prior to surgery, on the time taken for recovery and the final outcome.

In general it is agreed that rapid removal of extruded disc material facilitates a more complete and rapid recovery (McKee, 1992). Dogs with a shorter duration of clinical signs prior to surgery and a gradual onset of neurological dysfunction (<48 hours) have a quicker recovery (Brown et al., 1977; Gambardella, 1980). However, a recent study of 71 paraplegic dogs with intact deep pain sensation demonstrated that although a shorter duration of signs was indeed associated with a shorter recovery time, the rate of onset of clinical signs did not influence the recovery time. This study also reported that animals that showed clinical signs for more than 6 days took significantly longer to recover. However, the rate of clinical sign onset has been reported to influence the final outcome (Ferreira et al., 2002). Similarly, Scott and McKee (1999) demonstrated that peracute onset of signs indicated a poorer prognosis for dogs with no deep pain perception. Knecht (1970) compared the outcome of dogs after hemilaminectomy with the duration of clinical signs and concluded that delay before surgery does not influence outcome in dogs with mild neurological dysfunction but does affect functional recovery in paraplegic dogs. When performed within 12 hours of clinical sign onset,

hemilaminectomy in paraplegic dogs had a higher success rate.

## Type II intervertebral disc disease

Clinical signs: The clinical signs of Hansen type II IVDD include slowly progressive pelvic limb weakness, reluctance to rise or jump on furniture and difficulty climbing stairs. Onset of clinical signs is considered chronic and progressive. Localization is focal with asymmetrical or symmetrical weakness. Paraspinal hyperaesthesia may or may not be present.

Pathogenesis: Hansen type II disc disease is annular protrusion caused by shifting of central nuclear material and is commonly associated with fibroid disc degeneration (see Chapter 14). The annulus fibrosus slowly protrudes into the spinal canal to cause spinal cord compression. Type II IVDD usually occurs at the mobile points of the spinal column and is more common in older, non-chondrodystrophoid breeds of dog.

*Diagnosis:* The diagnosis may be suspected on routine spinal radiographs that show the presence of degenerative changes in the spinal column, such as spondylosis. Myelography, CT myelography or MRI are necessary to locate the spinal cord compression (Figure 15.12).



## 15.12

Ventrodorsal myelographic view of an extradural compression at the L1–L2 intervertebral disc interspace (arrowed).

## Treatment and prognosis:

Conservative management: Medical therapy is indicated in animals with early onset of type II IVDD and mild deficits. It also is indicated in those animals that are concurrently afflicted with suspected degenerative myelopathy. Medical therapy involves administration of NSAIDs or prednisolone. The use of a muscle relaxant such as diazepam or methocarbamol should

be considered in patients with spinal hyperaesthesia (see Chapter 13). Clinical signs do not always respond to medical therapy and often return after discontinuation of these therapies. Surgical decompression may offer a better long-term outcome.

Surgical management: The type of surgical decompression depends upon the location of the lesion. A hemilaminectomy is performed for lesions in the thoracic spine and lumbar spine cranial to L5. A dorsal laminectomy is performed if the lesion is located in the lumbosacral area. Typically type II disc protrusions require more spinal cord manipulation to relieve the compression from the annulus. The protrusion is usually excised; however, decompression by laminectomy alone may also be adequate in cases where the disc material is irretrievable. Often the neurological status of the animal is worse after surgery but this is usually temporary. Surgery may not be beneficial for those dogs with severe clinical signs that have progressed over several months because of irreversible neuronal loss consequent to the chronic compression.

If surgery is instituted early, prognosis is usually fair to good when patients are considered refractory to medical therapy. If the disease has coursed for several months and is associated with severe neurological signs (i.e. paraplegia) the prognosis is considered guarded.

#### Feline intervertebral disc disease

Intervertebral disc extrusions in cats causing secondary clinical signs of cervical and thoracolumbar myelopathy have been documented. However, clinically significant IVDD degeneration in cats is rare when compared with dogs.

Clinical signs: Clinical signs due to disc disease in cats are not common; the signs may reflect a painful transverse myelopathy at any region of the spinal cord but the probability of clinically significant disc extrusion seems to be higher in the thoracolumbar and lumbar area. Clinically significant intervertebral disc extrusion has been reported in cats <5 years of age but is more common in middle-aged to older cats (Bagley et al., 1995; Knipe et al., 2001; Muñana et al., 2001).

Pathogenesis: Hansen type I and II IVDD has been observed in cats, with type II being the more common. However, these are usually discovered as incidental findings at necropsy (King and Smith, 1964). Ventral annular protrusions and degenerative changes were commonly observed especially in the caudal thoracic and lumbar spinal regions (King and Smith, 1960). Age-related studies of disc degeneration in cats between 10 weeks and 18 years of age, that had no clinical signs of disc disease, showed that dorsal degenerative changes were most marked in the thoracic region followed by the cervical spinal region; and that ventral degenerative changes were more marked in the lumbar region. It was also shown that most older cats with intervertebral disc protrusions had multiple

lesions and that frequency increased with age. Hansen type I extrusions tended to predominate at the thoracolumbar junction (Rayward, 2002), although one study found the peak incidence at L4–L5 (Muñana *et al.*, 2001).

**Diagnosis:** Similar techniques for the diagnosis of disc disease in dogs apply for cats (see above).

Treatment and prognosis: Medical and surgical techniques for the treatment of disc disease in dogs also apply for cats but there have been no large studies published that evalute and compare the relative success of medical or surgical therapy in cats. Response to surgical treatment for type I IVDD can be excellent although it is obviously dependent on the severity of the initial injury (Knipe et al., 2001; Muñana et al., 2001; Rayward, 2002). Decompressive surgical techniques promote a more rapid and complete clinical recovery and definitively determine the diagnosis.

## Spondylosis deformans

*Clinical signs:* Spondylosis rarely causes neurological signs (see Chapter 13).

Pathogenesis: Spondylosis deformans is characterized by formation of bony growths and bridges at the intervertebral spaces. The condition is a common radiographic finding in older dogs along the thoracic and lumbar spine (Larsen and Selby, 1981; Kornegay, 1986). Most likely spondylosis is associated with degeneration of the annulus fibrosus of the intervertebral disc. Presence of spondylosis deformans has been associated with type II IVDD and degenerative LSS; however, these diagnoses are often made independent of the presence of spondylosis.

**Diagnosis:** The lesion is radiographically characterized (Wright, 1980; Romatowski, 1986). The osteophyte formation usually does not compress the neural tissue or encroach within the vertebral canal (Figure 15.13).



Lateral myelogram of the spine demonstrating severe spondylosis but no compression of the spinal cord. The myelogram shows extradural filling and is difficult to interpret properly.

**Treatment and prognosis:** NSAIDs or steroids have been reported to lessen spinal discomfort in animals with severe ankylosing spondylosis.

Spondylosis deformans is usually an incidental finding and is rarely associated with clinical signs, therefore the prognosis is good.

#### Spinal synovial cysts

**Clinical signs:** Clinical signs are consistent with a progressive myelopathy and include paraspinal hyperaesthesia.

**Pathogenesis:** Spinal synovial cysts occur in the cervical spine (see Chapter 14) of young large-breed dogs but more commonly involve the thoracolumbar region in older large-breed dogs (Perez et al., 2000; Dickinson et al., 2001b). Spinal extradural synovial cysts and ganglion cysts arise from the articular facets. Some authors have referred to both structures as intraspinal cysts due to the confusion of tissue origination (Perez et al., 2000). Pathogenesis of synovial cysts has been associated with degenerative disease and trauma. Increased mechanical stress and joint motion may predispose the thoracolumbar junction to osteoarthritis and synovial cyst formation. Histopathology of the cyst reveals fibrous connective tissue with a synovial cell lining.

**Diagnosis:** Radiographic findings include degenerative changes and remodelling of the articular processes. Myelography demonstrates spinal cord compression especially on the ventrodorsal view with attenuation of the contrast column medial to the articular processes. Attenuation of the ventral and dorsal columns (giving an hourglass appearance) is also present on lateral projections. The lesion is better defined using CT myelography and MRI. Albuminocytological dissociation is a consistent finding on lumbar CSF analysis.

**Treatment and prognosis:** The treatment often involves surgical decompression and excision of the cyst. Surgical intervention is indicated with severe neurological deficits and refractory pain. A hemilaminectomy is often performed if one side is affected. The cyst and any protruding disc material are removed.

Marked improvements in gait and neurological deficits occur post-surgically.

#### Calcinosis circumscripta

Calcinosis circumscripta (tumoral calcinosis) is an unusual disease that affects young dogs. Mineralization of the soft tissues of the spine (typically the ligamentum flavum) causes compression of the underlying spinal cord. The most common site of these lesions is dorsal to C1–C2 and a full discussion of this disease can be found in Chapter 14. However, cranial thoracic lesions that cause spinal hyperaesthesia and paraparesis have been reported, in particular in German Shepherd Dogs.

## Mucopolysaccharidosis

Clinical signs: The major forms of mucopolysaccaridosis (MPS) seen in cats are type I, VI and VII and in dogs are type I, II, III A and B, VI and VII (March, 2001). These diseases are characterized by multisystemic abnormalities which include skeletal, ocular, hepatic, splenic and CNS. The axial and appendicular skeletons are affected most severely causing facial and limb deformities. MPS VI causes bony proliferative lesions of the thoracolumbar spine leading to secondary

compressive myelopathy, most commonly from T12–L2 (Haskins *et al.*, 1980, 1983). Necropsy demonstrates bony fusion in the cervical, thoracic and lumbar vertebrae.

**Pathogenesis:** MPS comprises a group of lysosomal diseases that result from defects in metabolism of certain glycosaminoglycans or acidic mucopolysaccharides, which accumulate in connective tissue and brain. The genetic defect of MPS in dogs and cats is considered to be recessively inherited.

*Diagnosis:* A diagnosis of MPS is suspected based on clinical signs and signalment. Radiography of the spine reveals bony proliferation. The lesions are better defined by myelography and CT. Definitive diagnosis can be made by measuring lysosomal enzyme activity in leucocyte pellets, frozen liver, serum or cultured skin fibroblasts. DNA testing is available for some forms of MPS (Ray *et al.*, 1998) (see Appendix 1). The toluidine blue spot test for urinary sulphated glycosaminoglycans is positive. In some forms of MPS circulating neutrophils contain metachromatic granules when stained with toluidine blue.

Treatment and prognosis: Surgical correction of the spinal cord compression is performed by dorsal or hemilaminectomy to ameliorate signs of compressive myelopathy associated with MPS VI (Haskins et al., 1980, 1983). Some forms of MPS have been partially corrected after allogeneic bone marrow transplantation (Gasper et al., 1984; Byers et al., 1997). Haemopoietic stem cell gene therapy has produced clinical improvement in dogs with MPS VII but not in dogs with MPS I (Byers et al., 1997).

The prognosis is considered guarded for dogs and cats with spinal cord compression secondary to MPS.

#### **Anomalous diseases**

#### **Dermoid sinus**

Clinical signs: Dermoid sinuses more often occur in the cervical region but can involve the thoracolumbar region (Selcer et al., 1984; Fatone et al., 1995). Neurological examination is normal in the non-communicating form but neurological signs may occur if the sinus communicates with the dura or becomes infected (Selcer et al., 1984). Neurological signs reflect the neuroanatomical localization of the sinus. Close inspection of the hair on the midline may reveal abnormal placement.

**Pathogenesis:** Dermoid sinus is an inherited neural tube defect in the Rhodesian Ridgeback (Gammie, 1986) but has also been reported in other breeds (Selcer *et al.*, 1984; Fatone *et al.*, 1995; Cornegliani *et al.*, 2001). The defect results from incomplete separation of the skin and neural tube during embryonic development (Bailey and Morgan, 1992). The sinus often extends from the skin to the supraspinous ligament as a closed sac filled with keratin debris. Communication with the subarachnoid space can predispose to meningomyelitis.

**Diagnosis:** Diagnosis is based on physical examination; radiography can be used to evaluate the extent of the sinus. Contrast radiography, using a non-ionic contrast medium (e.g. iohexol), determines whether the tract is closed and non-communicating or open and communicating with the spinal canal. Myelography determines the amount of spinal cord displacement. MRI or CT may define other neural tube defects in a communicating dermoid sinus (Figure 15.14).





T2-weighted MR image of the thoracic spine of a 3-year-old male German Shepherd Dog with a dermoid cyst, spina bifida, meningocele and myelodysplasia at T5–T6. (a) Sagittal view. There is widening of the vertebral canal with dorsal displacement of the spinal cord, which appears to be pulled against the roof of T5–T6. The dura is displaced dorsally and protrudes between the abnormal dorsal spinous processes of T5 (due to spina bifida) and continues as a thin hypointense column to the surface of the skin.

(b) Transverse view. The displacement of the dura is also evident with this view. There is a depression in the skin's surface (arrowed) where the dura makes contact.

**Treatment and prognosis:** The treatment requires surgical excision (Gammie, 1986). A laminectomy is required for complete dissection of the sinus from the involved dura.

The prognosis is excellent in patients that have no neurological signs and no associated communication between the sinus and the spinal cord. Residual neurological deficits may be present if the spinal cord is involved.

#### Osteochondromatosis

*Clinical signs:* Clinical signs are reflected as pain and loss of function during active bone growth. Progressive paraparesis is the most common neurological finding.

**Pathogenesis:** Osteochondromatosis, known also as multiple cartilaginous exostoses, has been described in young dogs, cats and horses (Finnie and Sinclair, 1981; Reidarson *et al.*, 1988). Bony growths arise in any bone formed by endochondral ossification. Outgrowths are related to the metaphysis of growing bones. Lesions are present in the axial and appendicular skeleton. Vertebral involvement is common in dogs.

*Diagnosis:* The bony lesions are characterized radiographically as variably sized circumscribed radiopaque densities with radiolucent areas (see Chapter 5). CT can aid in the characterization of osteochondromas (Caporn and Read, 1996). Definitive diagnosis is made by histopathology.

**Treatment and prognosis:** The masses should be surgically excised if there is appendicular or neurological dysfunction (Caporn and Read, 1996).

Prognosis is dependent on the severity of the neurological deficits at presentation. The exostoses usually stop growing after closure of the physes and so the surgical removal of the masses, if spinal cord compression is occurring, can result in a successful outcome, but prognosis is dependent on the severity of neurological signs at presentation.

#### Vertebral anomalies

Clinical signs: Vertebral anomalies are often minor and usually cause no clinical signs. Malformations involving the spinal cord are more likely to cause neurological deficits, the nature of which is determined by the location of the abnormality.

**Pathogenesis:** Vertebral anomalies are common in the 'screw-tailed' breeds of dog such as Bulldogs and Boston Terriers, and the 'tail-less' cat, the Manx (see Chapter 18). Spinal cord and vertebral anomalies have been classified by Bailey (1975) into two major groups (Figure 15.15) based on embryological origin:

- Abnormalities originating in the tissues of mesodermal origin (vertebrae and intervertebral discs)
- Abnormalities originating from the tissues of ectodermal origin (spinal cord and meninges).

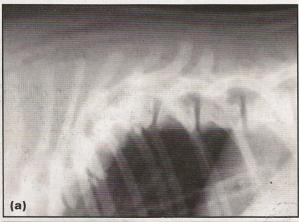
Mesodermal anomalies involve failure of vertebral separation or fusion. Important diseases are described in more detail below.

**Diagnosis:** The diagnosis is suspected based on clinical signs, age and breed. Diagnosis of vertebral anomalies is based on survey radiographic findings (Figure 15.16). Myelography is useful for determining extent of compression, stenosis or other possible spinal cord deformities (Knecht *et al.*, 1979). MRI is more sensitive for determining spinal cord involvement.

## Chapter 15 Paraparesis

Malformation	Type of abnormality	Clinical signs		
Malformations of the ve	rtebral body and intervertebral disc	The second secon		
Block vertebrae Lack of segmentation of somites and fusion of adjacen vertebrae		Rarely of clinical significance; may cause spinal stenosis		
Butterfly vertebrae	Sagittal cleft in the vertebral body due to presence of notochordal remnants	Incidental finding; common in brachycephalic, screw-tailed breeds		
Hemivertebrae	Failure of ossification in part of the vertebral body and lack of vascularization	Scoliosis, lordosis and kyphosis; compressive myelopathy; instability		
Transitional vertebrae Vertebrae with characteristics of adjacent divisions of vertebral column		Usually not clinically significant; sacralization of the lumbar vertebrae has been associated with lumbosacral syndrome		
Spinal stenosis  Can occur with congenital anomalies. The vertebral column is small due to reduced pedicle size or excessive facet size		May cause compressive myelopathy		
Malformations of the sp	inal cord and meninges			
Spina bifida occulta	Defect involving only incomplete closure of one or more vertebral arches	Usually an incidental radiographic finding		
Spina bifida (manifesta, cystica or aperta)	A defect in the vertebral arch with protrusion of meninges with or without spinal cord structures	Manifesta: implies associated clinical signs Cystica: implies meningocele or meningomyelocele Aperta: lesion communicates with environment		
Meningocele	Herniation of meninges from the vertebral canal through the bony defect; spinal cord remains in canal			
Meningomyelocele	The meningeal sac contains the spinal cord	Usually associated with severe neurological deficits; may be identified as a dorsal midline mass		
Sacrocaudal dysgenesis	Defective or absent formation of sacral or spinal cord segments	Associated with severe neurological impairment (typically S1–S3)		
Rachischisis  Vertebral canal opened the entire length; contents of spinal cord exposed		Often not compatible with life		

15.15 Vertebral and spinal abnormalities of the spine.





(a) Kyphosis and multiple vertebral anomalies of the thoracic region of the spine. (b) Block vertebral anomaly of the fourth and fifth lumbar vertebrae (arrowed). (Courtesy of Dr M. Walker, Texas A&M University)

**Treatment and prognosis:** If clinical signs are non-progressive, conservative management is recommended. Decompressive surgery is recommended with clinical signs of compressive myelopathy. Likewise, spinal instability and malalignment require vertebral stabilization techniques.

The prognosis is good for most vertebral anomalies because the majority of cases do not produce clinical signs. The prognosis is considered guarded if signs of spinal cord dysfunction are present. Multiple anomalies may exist concurrently.

## Parenchymal spinal cord malformations

Malformations involving the spinal cord parenchyma are often referred to as myelodysplasia. This term also refers to a number of abnormalities of embryological development including spinal dysraphism and syringomyelia (Dewey, 2003). Dysraphisms are congenital defects that result from the failure of the neural tube to close; however, no fusion defects have been documented. Conditions affecting the vertebral column and/or the spinal cord include spinal dysraphism, syringomyelia, spina bifida with or without meningomyelocele and caudal vertebral hypoplasia (see Chapter 18).

Spinal dysraphism: Spinal dysraphism was first documented in the Weimaraner (McGrath, 1965) but has been described in many other breeds including the Rottweiler (Shell et al., 1988), Dalmatian (Neufeld and Little, 1974), Alaskan Malamute (Rishniw et al., 1994), Chihuahua (Chesney, 1973) and Golden Retriever (Malik et al., 1991).

Clinical signs: Characteristic clinical signs include a hopping gait, crouched stance, wide-based stance and reduced postural reactions. Head tilt, tail abnormalities and scoliosis have also been recognized in some dogs. Scoliosis is a reflection of denervation muscle atrophy subsequent to damage to the grey matter and associated LMN signs. Signs are evident as early as 4–6 weeks of age. There is a poor correlation between severity of histopathological lesions and clinical signs. Clinical signs often remain static.

Pathogenesis: Spinal dysraphism is thought to be inherited in the Weimaraner as a co-dominant lethal gene (Shelton, 1977). Histopathology of the spinal cord reveals asymmetry of grey matter with neuronal ectopia and syringohydromyelia.

*Diagnosis:* Survey spinal radiography may reveal evidence of scoliosis. Syringomyelia is detected by MRI. Definitive diagnosis is based on histopathology (Figure 15.17).

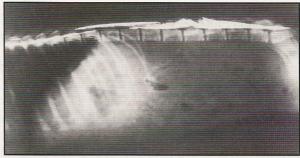


15.17

Transverse section of the spinal cord of a dog with syringomyelia (arrowed) and hydromyelia (arrowhead). Haematoxylin and eosin stain; original magnification X40. (Courtesy of Dr G.E. Lees, Texas A&M University)

Treatment and prognosis: There is no treatment for this disorder. As clinical signs often remain static the prognosis depends on the functional capabilities of the dog for its resultant quality of life.

Syringohydromyelia: Syringomyelia refers to a disease where a tubular cavitation filled with CSF extends through many spinal cord segments (see Figures 15.17 and 15.18). Hydromyelia is characterized by accumulation of CSF within an enlarged central canal of the



15.18 Lateral myelographic view of syringohydromyelia of the lumbar spinal cord region. (Courtesy of Dr G.E. Lees, Texas A&M University)

spinal cord. These diseases occur most commonly, but not exclusively, in the cervical spinal cord and are described in full in Chapter 14.

## Spinal stenosis

*Clinical signs:* Neurological signs reflect the neuroanatomical localization of the stenosis. Onset is usually insidious and progressive.

Pathogenesis: Congenital spinal stenosis indicates a malformation of the spine present at birth and occurs as a primary lesion or in association with other anomalies that predispose to stenosis (Bailey and Morgan, 1992). Relative stenosis refers to canal narrowing that does not cause compression of neural tissue; whereas, absolute stenosis refers to a stenosis causing spinal cord compression (Bailey and Morgan, 1992). Doberman Pinschers have a relative stenosis that most commonly involves the cranial thoracic vertebrae (T3–T6) (Bailey and Morgan, 1992). Spinal cord compression usually is not evident on myelography.

**Diagnosis:** A diagnosis is based on plain film radiography that defines associated vertebral anomalies but requires myelography to determine the presence of stenosis. MRI of the spinal cord is recommended to further delineate associated neural tissue anomalies or abnormalities (Figure 15.19).



Transverse T2-weighted MR images of the thoracic spine showing a normal canal (left) and a stenotic canal (right). Note the deformation of the spinal cord as a result of dorsal compression.

**Treatment and prognosis:** Surgical decompression may relieve the compression; however, associated vertebral and spinal cord anomalies need to be taken into account.

The prognosis is considered guarded due to chronicity and presence of other anomalies. The lack of information available with regard to surgical follow-up makes it difficult to give an accurate prognosis.

## Metabolic diseases

#### **Endocrine** neuropathies

Diabetes mellitus can be associated with a peripheral neuropathy (predominantly in cats). This disease is described fully in Chapter 14, but it is important to note that the sciatic nerves tend to be affected first and most obviously causing pelvic limb weakness and a plantigrade stance. Appearance of signs in the pelvic limbs first is also a feature of hypothyroid and insulinoma paraneoplastic neuropathy in dogs (see Chapter 14).

## Neoplastic diseases

Certain spinal cord neoplasms have a predilection for the thoracolumbar spine. Tumours can involve the vertebral body causing secondary spinal cord compression. Tumours affecting the spinal cord are described based on their location as extradural, intradural—extramedullary and intramedullary (Luttgen et al., 1980; Gilmore, 1983) (Figure 15.20; see also Chapter 13). Tumours of extradural location include primary bone tumours, metastatic tumours and lymphoma. Intradural—extramedullary tumours that occur include meningioma, neuroepithelioma and





Lateral myelographs. (a) Extradural compression with ventral and dorsal compression of the contrast column. The diagnosis of an undifferentiated sarcoma was confirmed by surgery. (b) Intramedullary swelling over the T13 ventral body is suggestive of an intramedullary neoplasm.

nerve sheath tumours. Intradural metastasis can also occur although it is extremely rare. Intramedullary tumours include glioma (oligodendrogliomas, astrocytomas), ependymoma and metastatic tumours (e.g. lymphoma, haemangiosarcoma) (Waters and Hayden, 1990).

## Vertebral body tumours

Clinical signs: Clinical signs may be focal or multifocal depending upon the extension of the tumour. Signs include pain and paraparesis or paralysis. Pathological fractures of the vertebral body result in an acute onset of neurological deficits.

Pathogenesis: Vertebral body tumours are primary or metastatic tumours most frequently reported in large and giant-breed dogs. Commonly described tumours include: osteosarcoma; fibrosarcoma; chondrosarcoma; haemangiosarcoma; plasma cell tumour; carcinoma; lymphoma; and liposarcoma (Morgan et al., 1980; Cooley and Waters, 1997; Levy et al., 1997). Small-breed dogs have a higher rate of vertebral metastasis than large-breed dogs (Cooley and Waters, 1997). Primary vertebral body tumours will cause a secondary myelopathy by compression or direct spinal cord invasion.

*Diagnosis:* The diagnosis is often based on survey radiographic findings, such as lysis, and pathological fractures secondary to tumour destruction of the bone (see Chapter 5). Other supportive diagnostic techniques, such as CT, MRI and myelography, are used to determine lesion extent (see Chapter 5) (Drost *et al.*, 1996; Kippenes *et al.*, 1999). Scintigraphy can be used to detect multiple metastases. Fluoroscopic-guided needle aspiration or surgical biopsy can be used to obtain a definitive diagnosis.

**Treatment and prognosis:** Palliative treatment options include surgery, irradiation therapy, chemotherapy or various combinations of the three. A vertebrectomy with a bone allograft fusion has been used for the treatment of a primary vertebral neoplasm in a dog (Chauvet *et al.*, 1999). Decompression or stabilization techniques are used in patients that are rapidly deteriorating.

The overall prognosis is considered guarded for dogs with vertebral neoplasia. Survival is not impacted greatly by various treatments but is often determined by the neurological deficits at the time of diagnosis (Dernell *et al.*, 2000).

#### Vertebral plasma cell tumours

**Ctinical signs:** Paraspinal pain and neurological deficits related to the location of the neoplasia are common neurological signs.

**Pathogenesis:** Plasma cell tumours have a predilection for the marrow of the axial skeleton. The two types of plasma cell tumour of the spine are the disseminated form (multiple myeloma) and the focal form (plasmacytoma) (Rusbridge *et al.*, 1999). Multiple myeloma is

characterized by proliferation of plasma cells within the bone marrow, with or without other organ involvement (Vail, 2000). The neoplastic cells secrete paraproteins causing a monoclonal gammopathy. The disease is associated with other paraneoplastic syndromes. Solitary plasmacytomas have been described infrequently in dogs.

**Diagnosis:** The diagnosis of multiple myeloma requires demonstration of two or more criteria (Vail, 2000):

- Radiographic evidence of osteolytic lesions
- A bone marrow biopsy with >5% plasma cells
- Monoclonal gammopathy in serum or urine
- · Light chain (Bence-Jones) proteinuria.

Immunoperoxidase staining for monoclonal immunoglobulin should be conducted on tissues from patients with non-secretory disease (Marks et al., 1995). Diagnosis of a plasmacytoma requires a biopsy-proven plasma cell tumour; a normal bone marrow biopsy; normal results of serum and urine protein electrophoresis; absence of other lesions on radiographs; and absence of blood dyscrasias.

**Treatment and prognosis:** Chemotherapy is the mainstay treatment for multiple myeloma. In solitary plasmacytomas, irradiation therapy with chemotherapy is the optimal treatment (Rusbridge *et al.*, 1999). Surgical excision may also be effective for management but may be limited if it is incomplete.

Chemotherapy with radiation therapy has been shown to decrease metastasis and prolong survival time. Solitary plasmacytomas may represent an early state of multiple myeloma. Since these tumours are both chemosensitive and radiosensitive they carry a better long-term prognosis than other secondary tumours (Rusbridge *et al.*, 1999).

#### Spinal neuroepithelioma

Clinical signs: Clinical signs of spinal neuroepithelioma (nephroblastoma) are dependent on tumour location. The most common neurological findings include progressive paraparesis and ataxia. Clinical signs of spinal neuroepitheliomas consist of a progressive asymmetrical T3–L3 myelopathy.

Pathogenesis: Canine neuroepithelioma is an intradural—extramedullary neoplasm in young dogs located between T10 and L2 in the spinal cord. Occasionally this tumour is extradural or intramedullary. The origin of the tumour is unknown but descriptions have included medulloepithelioma, embryonal nephroma, nephroblastoma and Wilm's tumour. Primary spinal neuroepithelioma is thought to arise from embryonic tissue trapped within the dura during fetal development. Histological appearance may vary. Usually neuroepithelioma involves one kidney or the spinal cord, but not both. Rarely renal nephroblastoma will secondarily metastasize to the spinal cord, bone marrow and spinal canal (Gasser et al., 2003).

**Diagnosis:** Survey radiography of the spine shows no abnormalities. Myelography is useful for determining location and lesion extent. CT or MRI of the spine can better assess vertebral and spinal cord involvement. Abdominal radiography and ultrasonography can assess for primary renal involvement if present. Immunohistochemistry is used to identify the mesenchymal or epithelial components of neuroepithelioma.

Treatment and prognosis: If detected early, surgical excision can lead to long-term palliative therapy with limited morbidity (Moissonnier and Abbott, 1993; Macri et al., 1997). Adjunct irradiation is considered when total surgical resection is not possible (Dickinson et al., 2001a).

Overall prognosis is uncertain because of the limited number of cases reported. Prognosis is considered guarded because spinal cord involvement is often extensive by the time of diagnosis. Long-term prognosis is poor because of tumour recurrence.

#### Spinal lymphoma

Extradural lymphoma is the most common tumour to induce spinal cord dysfunction in cats.

**Clinical signs:** Neurological signs are related to the location of the lymphoma and are often insidious but there can be an acute exacerbation with rapid deterioration.

Pathogenesis: Feline leukaemia virus has been implicated and is an important factor associated with lymphoma in young cats (Spodnick et al., 1992; Lane et al., 1994). Feline spinal lymphoma has a predilection for the thoracic and lumbar spinal cord (Lane et al., 1994). Most affected cats are <2 years of age but older animals may also be affected (Spodnick et al., 1992; Lane et al., 1994). Renal lymphoma is likely to relapse in the CNS (Mooney et al., 1987). Lymphoma is the most commonly diagnosed malignant tumour in dogs but involvement of the nervous system is relatively unusual. Involvement of the CNS is more common than the peripheral nervous system in both dogs and cats.

Diagnosis: The safest and most reliable method of obtaining a diagnosis of lymphoma in the CNS may be by confirming the presence of lymphoma in other organ systems (Noonan et al., 1997). The abdominal organs and bone marrow are commonly aspirated but may not be affected. CSF analysis may detect the presence of malignant lymphocytes but lack of this finding cannot rule out CNS involvement. Survey spinal radiography may detect bone involvement. Myelography is useful for determining lesion extent and determining extradural, intradural-extramedullary or intramedullary involvement. Spinal lymphoma is detected most commonly as an extradural lesion. MRI may detect intramedullary lesions. A definitive diagnosis can be determined from the cytological examination of the contents of fluoroscopic-guided fine needle aspirations or a surgical biopsy (Figure 15.21).



Necropsy finding in a cat of an extradural mass causing severe spinal cord compression. The mass was confirmed by histopathology to be a lymphoma.

**Treatment and prognosis:** Therapies, used in combination or alone, include surgical resection, focal irradiation, and systemic chemotherapy (e.g. cytarabine or methotrexate (see Chapter 22) and corticosteroids) (Noonan *et al.*, 1997). A laminectomy procedure provides an accurate histological diagnosis and adequate decompression. Surgical treatment is necessary for cats that fail to respond rapidly to chemotherapy.

Duration and remission times vary among studies. Intramedullary lymphoma is difficult to treat because of poor penetration across the blood—brain barrier of some chemotherapeutic agents. Effectiveness of chemotherapy for lymphoma with neural involvement still remains to be determined. In general, the prognosis for pelvic limb paresis or paralysis in cats is guarded to poor. The median duration of complete or partial remission in six cats with spinal lymphoma and severe neurological deficits, treated with vincristine sulphate, cyclophosphamide and prednisolone, has been reported as 14 weeks (range 5–28 weeks) and 6 weeks (range 4–10 weeks), respectively (Spodnick *et al.*, 1992).

#### **Nutritional diseases**

## Hypervitaminosis A

This is a rare cause of paraparesis in cats and is discussed in Chapter 13.

## Inflammatory diseases

#### Discospondylitis

Discospondylitis refers to an infection of the intervertebral disc and its contiguous vertebrae. Involvement of the thoracolumbar spine is an important cause of paraparesis but as the most common initial sign is pain, discospondylitis is discussed in full in Chapter 13.

## Spinal empyema

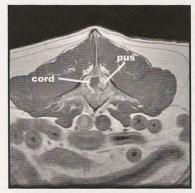
**Clinical signs:** Characteristic clinical signs are a high fever, acute progressive spinal hyperaesthesia and progressive myelopathy.

**Pathogenesis:** Spinal empyema is defined as an extensive accumulation of purulent material in the epidural space of the vertebral canal (Dewey *et al.*, 1998). This is an uncommon condition also reported in humans after spinal epidural anaesthesia, spinal surgery or haematogenous spread. Direct extension of osteomyelitis is another cause of the infection.

*Diagnosis:* Haematology reveals an inflammatory leucogram. Blood cultures can be positive. *Staphylococcus* and *Streptococcus* species are commonly isolated. Radiography may reveal vertebral physitis or discospondylitis. Extensive epidural lesions have been identified on myelography (Figure 15.22) (Dewey *et al.*, 1998). Advanced imaging can help to assess the extent of neural involvement and guide surgical therapy (Figure 15.23).



Lateral myelographic view of the thoracic spine demonstrating an extensive epidural compressive lesion confirmed as spinal empyema. (Courtesy of Dr C.W. Dewey, Texas A&M University)



Transverse T1-weighted MR image of the lumbar spine of a 2-year-old Dalmation. The

15.23

spine of a 2-year-old Dalmation. The spinal cord is compressed by a lateralized mass of pus.

**Treatment and prognosis:** Effective treatment is rapid institution of an appropriate antibiotic therapy and surgical drainage of the epidural fluid (Jerram and Dewey, 1998).

The prognosis is considered guarded. The length of time the patient is non-ambulatory before antibiotic therapy is instituted is inversely proportional to the neurological recovery.

## Inflammatory spinal cord diseases

Inflammatory diseases of the meninges and CNS can also cause focal signs of paraparesis and plegia. Examples of infectious diseases include feline infectious peritonitis (FIP), canine distemper virus (CDV), feline immunodeficiency virus (FIV), protozoal, rickettsial, algal and fungal diseases (see Chapter 10). Non-infectious inflammatory diseases include granulomatous meningoencephalomyelitis (GME) (see Chapter 10), steroid-responsive meningitis and arteritis (see Chapter 13). Diagnosis of these disorders is supported by clinical presentation, CSF analysis, serology and necropsy examination.

## Canine distemper viral myelitis:

Clinical signs: Respiratory, enteric, neurological and ocular manifestations have been described in naturally occurring disease (Appel, 1969; Tipold et al., 1992; Thomas et al., 1993). Respiratory and enteric forms of the disease are more common in puppies or severely immunosuppressed adult dogs. Neurological signs whether acute or chronic are usually progressive (Tipold et al., 1992; Thomas et al., 1993). Neurological signs vary with the area of the CNS infected but spinal cord signs can predominate. Clinical signs of CDV myelitis are focal or diffuse with the T3-L3 spinal region more frequently involved. Paraspinal hyperaesthesia can occur as a result of meningeal inflammation. Myoclonus (involuntary twitching of muscles) can present without other neurological signs but as the spinal cord disease progresses there may be UMN signs in the affected limbs.

Pathogenesis: Canine distemper is a Morbillivirus within the family of Paramyxoviridae that can cause focal or diffuse lesions in both the grey and white matter of the CNS (Greene and Appel, 1998). Focal or diffuse demyelination can occur in the white matter of the spinal cord. Neurological forms often occur as the only clinical manifestation in dogs with intermediate levels of viral immunity. The type of lesion produced in the CNS depends upon host immunity and the age and duration of infection. The type of lesion ranges from acute polioencephalomyelopathy with glial and neuronal necrosis in immature or immunodeficient dogs to more chronic leucoencephalomyelopathy with demyelination in older or immunosuppressed dogs (Appel, 1969; Krakowka and Koestner, 1976; Higgins et al., 1982; Zurbriggen and Vandevelde, 1994). Demvelination is therefore a more prominent feature in the chronic stages of disease (Vandevelde et al., 1982).

Diagnosis: The diagnosis of CDV infection is based on history and clinical signs. A definitive antemortem diagnosis of CDV is difficult to obtain. Clinical laboratory findings and CSF analysis are often non-specific. Immunofluorescent techniques for CDV antigen on conjunctival tissue, CSF, urine, skin or blood can facilitate a diagnosis but lack sensitivity. Analysis of CSF-specific IgG levels and determining the CSF:serum ratio can be used to detect chronic CDV infections.

Treatment and prognosis: The treatment of CDV myelitis is often unsuccessful. Corticosteroid therapy of short duration may provide some remedy. Clinical signs typically wax and wane over time followed by a more rapid progression. The prognosis is considered poor for recovery.

# Feline infectious peritonitis, myelitis and meningitis:

Clinical signs: Most cats infected are <2 years of age but cats of any age can be infected (Addie and Jarrett, 1998). Clinical signs are often insidious

and present with focal, diffuse or multifocal distribution. Signs often are vague and reflect multiple organ system involvement. Systemic signs include pyrexia, weight loss, dullness and anorexia. Neurological signs with FIP are seen primarily with the non-effusive form of the disease. Commonly recognized spinal signs are pelvic limb or generalized ataxia and paraspinal hyperaesthesia (Legendre and Whitenack, 1975; Kline et al., 1994). Pathology of spinal cord disease includes hydromyelia and myelitis (Kline et al., 1994). Other areas of the CNS are also often involved (see Chapter 10).

Pathogenesis: FIP is a common viral disease in cats caused by the ubiquitous feline enteric coronavirus (Pedersen, 1995; Addie and Jarrett, 1998). FIP is an immune complex forming disease involving virus, antibodies and complement. Histological findings include granulomatous inflammation of the meninges, ependymal cells and choroid plexus (Kornegay, 1978). FIP occurs in two forms: (a) non-effusive (dry) and (b) effusive (wet).

Diagnosis: Confirmation of FIP ante-mortem is very difficult. Biopsy confirmation of infected tissue is the only method to definitively diagnose FIP. CSF analysis is abnormal with an elevated total nucleated cell count and protein levels (Kline et al., 1994). The white blood cell (WBC) differential often reflects a neutrophilic pleocytosis but cellular distribution can be variable. CSF protein concentration can be extremely elevated (1000–2000 mg/dl). Results of serological testing are difficult to interpret reliably. The most useful antemortem indicators of disease are a positive anticoronavirus titre in CSF, a high serum total protein concentration and findings on imaging that include periventricular enhancement, ventricular dilation and hydrocephalus (Foley et al., 1998).

Treatment and prognosis: No effective treatment is known. Use of corticosteroids and other immunosuppressive drugs may slow the progression of the disease. The prognosis of cats with FIP is poor.

Feline leukaemia virus-associated myelopathy: This disease has been reported in cats chronically infected with feline leukaemia virus (FeLV) (Carmichael et al., 2002). Clinical signs consist of hyperaesthesia and progressive paraparesis and paralysis. Light microscopic examination identifies swollen axons and myelin sheaths in the brainstem and spinal cord of affected cats. Immunohistochemical staining of affected tissues reveals FeLV antigens in neural tissue.

**Protozoal myelitis:** Toxoplasma gondii infection can cause a focal or disseminated myelopathy in dogs and cats (Dubey and Lappin, 1998). Meningoencephalomyelitis and myositis are common lesions associated with *Neospora caninum* (Dubey *et al.*, 1988) (see also Chapter 10). Rapid ascending myelitis is more common with *N. caninum* infection (Ruehlmann *et al.*, 1995). Many previously reported cases of *T. gondii* are now thought to be due to *N. caninum*.

Clinical signs: The neurological signs of protozoal infection reflect disseminated or progressive multifocal disease. Dogs as young as 4 weeks of age may develop a progressive asymmetrical or symmetrical paraparesis from T. gondii or N. caninum infections (Core et al., 1983; Hay et al., 1990; Ruehlmann et al., 1995). The organism infects the lumbosacral nerve roots and muscles and often causes a myelitis and/or meningitis (Cuddon et al., 1992). These dogs may have a 'bunnyhopping' gait or present with severe rigid extension of the pelvic limbs. The limbs are rigid because of muscle fibrosis and tendon contracture. The patellar and withdrawal reflexes are lost and severe muscle atrophy often ensues. Rarely, the disease progresses rapidly to tetraparesis and respiratory paralysis (Braund et al., 1988; Cummings et al., 1988; Ruehlmann et al., 1995).

Pathogenesis: Infection can occur in utero, by ingestion of oocysts (due to faecal contamination) or by ingestion of bradyzoites (in muscle). Although subclinical infection is common, clinically significant protozoal infections tend to occur in immunocompromised or young animals, and can affect muscle, peripheral nerves and the CNS (see Chapter 10).

Diagnosis: The diagnosis is suspected based upon history and clinical signs. Electromyography shows diffuse fibrillation potentials and sharp waves in the lumbar paravertebral and pelvic limb musculature. CSF analysis shows a mixed cell or mononuclear pleocytosis and an elevated protein concentration. Histology of the muscle and identification of the organism confirms the diagnosis. Serology for *T. gondii* and *N. caninum* is often positive, and polymerase chain reaction (PCR) of the CSF can confirm the diagnosis (Schatzberg et al., 2003).

Treatment and prognosis: Early treatment for 2–4 weeks with combinations of trimethoprim-sulfadiazine or ormetoprim sulfadimethoxine and clindamycin may improve clinical signs (Hay et al., 1990; Mayhew et al., 1991). Pyrimethamine may be added to the regimen but can cause bone marrow suppression in young animals.

Early antibiotic treatment may improve clinical signs but recovery is often incomplete. Poor prognostic indicators for resolution of clinical signs include rapidly progressive disease, signs of multifocal CNS disease, pelvic limb hyperextension and a long time interval between onset of clinical disease and treatment (Ruehlmann *et al.*, 1995).

#### Vertebral physitis

Clinical signs: Clinical signs include paraparesis, back pain and lethargy. A high incidence of urinary tract infections (UTIs) have coincided with a diagnosis of vertebral physitis.

**Pathogenesis:** Vertebral physitis is a condition separate from discospondylitis in young dogs. Bone lysis is confined to the caudal physeal zone of the infected vertebrae. Infection appears most likely to become established in the highly vascular, slow-flowing

metaphyseal and epiphyseal capillary beds (Jimenez and O'Callaghan, 1995). Establishment in the metaphyseal-physeal-epiphyseal area is more likely to lead to asymmetrical lesion distribution.

*Diagnosis:* Radiographic findings are usually confined to the lumbar vertebrae. Lesions initially occur at the caudal physis of the affected vertebral body. Radiographic findings include lucent widening of the caudal vertebral physis with loss of definition of the metaphyseal and epiphyseal margins of the physis; followed by increasing sclerosis in the cancellous bone, collapse of the physis and remodelling of the ventrocaudal aspect of the affected vertebra (Jimenez and O'Callaghan, 1995). Bacteria may be cultured from the blood and urine and from lesion aspirates.

**Treatment and prognosis:** Identification of the organism with culture and sensitivity studies (e.g. of urine) is helpful for determining an appropriate antibiotic regimen, which should be continued for 6–8 weeks.

The prognosis is considered good to excellent if the organism is susceptible to the antibiotic regimen.

## Idiopathic diseases

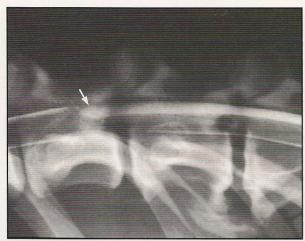
## Arachnoid cysts

**Clinical signs:** Clinical signs reflect a progressive T3 to L3 myelopathy that usually lacks paraspinal hyperaesthesia. Incontinence may be a prominent clinical feature.

Pathogenesis: Arachnoid cysts (also known as subarachnoid cysts, meningeal cysts, intra-arachnoid cysts, leptomeningeal cysts and arachnoid diverticula) can cause compression of the thoracolumbar spinal cord. Arachnoid cysts occur in the intradural—extramedullary space. It is proposed that these 'cysts' are actually diverticula in the intradural space (see also Chapter 14). Thoracolumbar arachnoid cysts more commonly occur over the caudal thoracic vertebrae (T11—T13) and may expand over two vertebrae (Skeen et al. 2003). Age of onset in dogs with thoracolumbar cysts is older than dogs with cervical cysts (Skeen et al., 2003). Spinal arachnoid cysts also occur in cats (Shamir et al., 1997; Vignoli et al., 1999).

**Diagnosis:** Myelography is useful for detecting the diverticula within the intradural space (Figure 15.24). On MRI the diverticula appear as focal, well circumscribed lesions that are isointense to CSF on both T1-weighted and T2-weighted images. MRI is more sensitive than CT in detecting associated intramedullary lesions such as syringomyelia (Galloway *et al.*, 1999).

**Treatment and prognosis:** Surgical decompression of the spinal cord is the recommended treatment. Dogs that have the cyst marsupialized may have a better long-term outcome than if the cyst is fenestrated (Skeen *et al.*, 2003). Conservative management is indicated in dogs with mild neurological deficits and includes anti-inflammatory doses of prednisolone and controlled exercise.



Lateral myelographic view of the caudal thoracic spine demonstrating a spinal arachnoid cyst and diverticula in the dorsal contrast column.

The prognosis is good for young dogs if treated within 4 months of development of clinical signs. Dogs that were older than 3 years of age, had clinical signs for a duration of >4 months and were treated with only fenestration of the cyst had a poor long-term outcome (Skeen *et al.*, 2003).

#### Disseminated idiopathic skeletal hyperostosis

Disseminated idiopathic skeletal hyperostosis (DISH) refers to extensive ossification through the axial and appendicular skeleton, including the vertebrae in dogs and cats (Morgan and Stavenborn, 1991; LeCouteur, 2000). This disorder is characterized by a proliferative bony response to minor stresses and is very rare. Radiographic signs are characterized by a flowing ossification primarily located at the ventrolateral aspect of the spine and extending for at least four contiguous vertebrae. The interspinous ligaments and the extraspinal ligamentous attachments may also be ossified. Neural involvement needs to be confirmed with the aid of advanced imaging as in the case of spondylosis deformans. Clinical signs of gait abnormalities and decreased joint mobility reflect the effects of periarticular involvement of the axial and appendicular skeleton. There is no known cure although surgical decompression of neural tissue may provide remission of the signs with likely recurrence.

## **Traumatic diseases**

# Fractures and luxations of the thoracolumbar spine

Clinical signs: The neurological signs are determined by the level of any associated cord damage. The neurological examination is unique in acute thoracolumbar injury; minimal manipulation is usually advised (see Chapter 19). Schiff—Sherrington posture is a common finding and indicates severe and acute injury of the thoracolumbar spinal cord region but is not a prognostic indicator. Superficial and deep pain nociception are carefully assessed in paraplegic animals to assist with determination of prognosis.

Pathogenesis: Automobile-related injury is the most common cause of exogenous trauma to the spine (Turner. 1987; Selcer et al., 1991). The thoracolumbar vertebrae are most commonly injured in dogs and cats. Fractures occur between T11 and L6 in 50-60% of patients after blunt trauma (Feeney and Oliver, 1980). Fractures in the thoracic spine may have little displacement because of the protection provided by the ribs, ligamentous support and epaxial musculature. Fractures and luxations of the thoracolumbar spine are often associated with other systemic injuries, i.e. pneumothorax, pulmonary contusions, orthopaedic injuries, urogenital injuries and diaphragmatic hernia. Approximately 20% of patients with thoracolumbar fractures have a second spinal column fracture-luxation (Feeney and Oliver, 1980). Primary mechanical injury to the neural tissue can subsequently lead to secondary biochemical injury (secondary injury theory - see Chapter 19). The amount of neural tissue injury is related to the rapidity and severity of insult and the amount and duration of compression.

*Diagnosis:* Results of the neurological examination are used to determine neuroanatomical localization and severity of the spinal cord injury. It is important to perform the neurological examination with care to prevent further injury and displacement of the spine. The neurological examination findings are most important in establishing the prognosis irrespective of radiographic findings.

Plain radiography of the entire spine should be performed. Two views are used while minimizing patient movement by obtaining the ventrodorsal view by horizontal beam (Figure 15.25). Results of plain



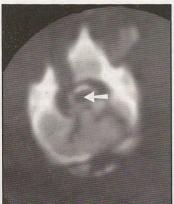


(a) Lateral view plain radiograph showing mild evidence of spinal displacement at L2 and L3 (arrowed).
(b) Ventrodorsal view plain film radiograph of the same spine showing lateral displacement of the vertebral bodies at L2 and L3. (Courtesy of Dr M. Mahaffey, University of Georgia)

radiography are used to determine the precise lesion location(s) and extent, demonstrate multiple lesions and determine an appropriate surgical procedure. Myelography is used, when the radiographic findings do not correlate with the neurological examination, to evaluate spinal cord swelling in concussive injuries and to further assess severity of spinal cord compression (Figure 15.26). CT or MRI is useful for further evaluating bone and spinal cord tissues, respectively (Figure 15.27).



15.26 Lateral myelographic view demonstrating spinal displacement of L2–L3 and spinal cord compression.



15.27

Transverse CT scan demonstrating a complete vertebral body fracture of T13 and displacement of all three compartments (dorsal, middle and ventral). The spinal cord is arrowed.

Spinal stability is assessed using a three-compartment theory; for further information see Chapter 19 (Shires *et al.*, 1991).

## Treatment and prognosis:

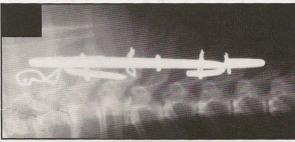
Conservative management: Priority is placed on treatment of extraneural injuries beginning with management of shock and haemorrhage. Management of an animal with spinal trauma focuses on the prevention of secondary injury to the spinal cord parenchyma. Principles of management of the acute spinal cord injury patient including the use of methylprednisolone sodium succinate are further addressed in Chapter 19.

Non-surgical management of spinal fractures consists of strict cage confinement for 6–8 weeks. Indications include minimal neurological deficits, minimal vertebral displacement and lack of myelographic evidence of spinal cord compression. The aim of external support is to provide immobilization of the vertebral segments cranial and caudal to the damaged area (Bagley *et al.*, 1999). It is important to follow principles of bandage care when using methods of external support. The patient will need to be turned regularly and kept clean and dry to prevent urine scalding.

Surgical management: This often provides a better chance for more rapid and complete neurological recovery. However, the role of surgery for spinal trauma remains unclear. Indications include severe neurological deficits and deteriorating neurological status, myelographic evidence of compression and damage of two or more spinal segments (Bagley, 2000). Timely surgical intervention is important to allow for maximal recovery. The objectives for surgical management of spinal trauma are decompression, realignment and stabilization (Sturges and LeCouteur, 2003). The decompressive procedure should be conservative so as not to disrupt further the integrity of the vertebrae, but large enough to allow for removal of compressive material (Schulz et al., 1996).

Methods of internal fixation are commonly used to stabilize spinal fractures. The method is dependent upon the size of the patient, fracture type and surgeon preference (Sturges and LeCouteur, 2003). Common techniques used for internal stabilization include securing plastic plates to the dorsal spinous processes, vertebral body plating, pins and/or screws and polymethylmethacrylate (PMMA), articular process stabilizing and vertebral spinal stapling. Spinal stapling using pins and wire is a widely used technique in smallsized patients (Figure 15.28). PMMA and Steinmann pin fixation is the preferred stabilization technique used by this author (Figure 15.29). Pins are used to anchor the PMMA to the bone (Blass and Seim. 1984; Garcia et al., 1994). Modification of pins and PMMA using screws has been described (Garcia et al., 1994; Bagley, 2000). Successful outcome after surgical fixation depends on the type and strength of fixation, the surgeons' skill and knowledge of the spinal anatomy, and the accuracy of vertebral column alignment.

Careful attention to postoperative care is imperative for the well-being of the patient (Tefend and Dewey, 2003). Potential complications include UTIs, decubital ulcers and failure of the implant. Physical therapy is important in the recovery process (see Chapter 24).



Lateral plain film radiograph showing the spinal stapling technique used to stabilize a T6–T7 spinal fracture in a cat.



Lateral plain radiograph showing the use of polymethylmethacrylate (PMMA) and Steinmann pin placement to stabilize a T13 fracture.

The prognosis for animals with acute thoracolumbar injury is dependent upon the results of the neurological examination. The prognosis for recovery from a spinal fracture or luxation that results in paraplegia with loss of deep pain perception is considered poor (Olby *et al.*, 2003). Patients that maintain pain perception may still require months to recover and have residual neurological deficits including urinary and/or faecal incontinence.

Futher discussion of traumatic diseases can be found in Chapters 14 and 19.

## **Toxic diseases**

Most toxicities that cause paraparesis do so by having an effect on peripheral nerve function and will often quickly progress to tetraparesis (see Chapter 14 for further information).

Antiepileptic drugs

High blood levels of antiepileptic drugs, i.e. phenobarbital and potassium bromide either used in isolation or combined, can produce hindlimb ataxia that can progress to tetraparesis. It is therefore recommended that blood levels of these drugs are evaluated in epileptic patients that are receiving treatment and have become paretic or ataxic.



Great Dane with an asymmetrical spinal cord lesion suggestive of fibrocartilaginous embolic (FCE) disease. Note the conscious proprioceptive deficit and atrophy of the biceps femoris muscle in the right pelvic limb.

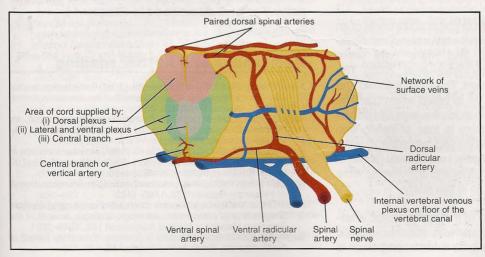
## Vascular diseases

## Fibrocartilaginous embolic myelopathy

Clinical signs: Neuroanatomical localization often is associated with the spinal cord intumescences but other spinal cord regions can be involved (Cauzinille and Kornegay, 1996). Thoracolumbar signs are more common than cervicothoracic. Clinical signs usually are associated with trauma or exercise. Asymmetrical lesion distribution (Figure 15.30) is a clinical feature due to the distribution of the blood vessels to the spinal cord parenchyma (Figure 15.31); however, the lesion can be symmetrical. Symmetrical lesions more often are associated with loss of nociception. Spinal hyperaesthesia can be present initially but is absent after the onset of ischaemia. Maximal neurological deficits usually occur within the first 24 hours. Dogs with lumbosacral intumescent involvement more often have loss of deep pain perception.

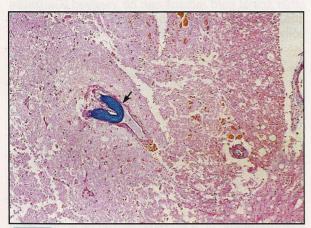
Pathogenesis: FCE is characterized by acute spinal cord infarction caused by embolism of fibrocartilage identical to that of the nucleus pulposus of the intervertebral disc (Griffiths, 1973). Many theories exist as to the pathophysiology for embolization (Penwick, 1989; Cauzinille, 1993). Entry of disc material into the vascular system and embolization from the point of entry to the arteries and veins of the spinal cord has yet to be elucidated. Non-chondrodystrophoid breeds are predisposed, which may relate to the disc being more gelatinous and prone to cause microextrusion. FCE is frequently recognized in large and giant breed dogs but also affects small- to medium-sized dogs (de Lahunta and Alexander, 1976; Cauzinille and Kornegay, 1996). Certain pure-bred dogs that have been documented with FCE include Miniature Schnauzers (Hawthorne et al., 2001), German Shepherd Dogs and Irish Wolfhounds (Junker et al., 2001). FCE is rare in cats (Scott and O'Leary, 1996; Abramson et al., 2002).

**Diagnosis:** The diagnosis is based on history, signalment and clinical signs. Early myelographic evidence of FCE is intramedullary spinal cord swelling (Gandini *et al.*, 2003). MRI may be a more sensitive technique



The spinal cord vascular supply demonstrating the approximate regions of the parenchyma which have differing arterial networks.

for detection of intramedullary lesions and rule out possible associations with intervertebral disc extrusions. CSF analysis may reveal abnormalities in severe cases. Diagnosis of FCE is confirmed by histopathology and documentation of nucleus pulposus in the spinal cord vasculature (Figure 15.32).



Transverse section of the dorsal funiculus of the spinal cord. An artery is occluded by Alcian blue-positive material (arrowed), suggestive of a cartilaginous substance. Note the degeneration of axons and myelin in the white matter of the spinal cord. (Courtesy of Dr B.R. Berridge, Texas A&M University)

**Treatment and prognosis:** Treatment is with medical and supportive care. Early in onset of FCE (≤8 hours) administration of methylprednisolone sodium succinate has been recommended (see Chapter 19). As for all spinal cord injuries, physical therapy is important in the process of recovery (Gandini *et al.*, 2003).

Recovery is dependent upon the extent of spinal cord damage. A poor prognosis has been correlated with involvement of the intumescences, symmetry of signs and decreased deep pain sensation (Cauzinille and Kornegay, 1996; Gandini *et al.*, 2003). Dog size and severity of clinical signs contribute to owners electing for euthanasia (Cauzinille and Kornegay, 1996). Animals with functional recovery within two weeks have a better prognosis; however, recovery may not be complete (Cauzinille and Kornegay, 1996).

## **Aortic thrombosis**

Clinical signs: Clinical signs consist of acute onset of an asymmetrical pelvic limb paresis and/or paralysis. Abyssinian, Birman, Ragdoll and male cats were overrepresented in one study (Smith et al., 2003). The femoral pulse is weak or absent. The limbs are cold and nail beds are cyanotic and fail to bleed when cut. The pelvic limbs are stiff and the muscles are hard and painful upon palpation. Typically there is loss of pelvic limb nociception distally. Tachypnoea and hypothermia were seen in 91% and 66% of 127 cats, respectively (Smith et al., 2003). Congestive heart failure and arrhythmias were each seen in over 40% of cats in this study.

**Pathogenesis:** Obstruction of the aortic or iliac arteries commonly occurs in cats with thromboembolic disease (Flanders, 1986). Aortic thromboembolism is

also known as saddle thrombi. The most frequent underlying disease in cats with thromboembolism is hypertrophic cardiomyopathy (Laste and Harpter, 1995; Smith *et al.*, 2003). Both restriction of blood flow by the embolus and release of vasoactive substances cause ischaemia to the sciatic nerve and muscles of the pelvic limbs.

*Diagnosis:* Aortic thromboembolism is suspected upon clinical signs. Common biochemical abnormalities in these cats include hyperglycaemia, azotaemia and a markedly elevated creatine kinase concentration soon after the embolic episode. Evidence of cardiac disease is further supported by physical examination findings, thoracic radiographs and echocardiography. Doppler ultrasonography of the aorta and its trifurcation can sometimes identify thrombotic disease.

Treatment and prognosis: Initially therapy involves management of the cardiac disease and supportive care. Cats benefit from administration of acepromazine maleate (ACP), heparin and analgesia. Use of ACP is controversial; although it may improve collateral blood flow and decrease anxiety, it may cause hypotension and current advice is to avoid its use. Specific therapies for the clot include surgical removal and thrombolytic agents; but risks versus benefits need to be considered. No significant difference has been found with survival or recurrence rate between cats receiving high-dose aspirin (>40 mg/cat q72h) and cats receiving low-dose aspirin (5 mg/kg q72h) (Smith et al., 2003). Given time the clot will undergo spontaneous thrombolysis.

Long-term prognosis for cats with aortic thomoboembolism is poor. A review of 100 cases reported that of the 37% of cases to survive the initial episode, the average long-term survival was 11 months (Laste *et al.*, 1995). A more recent review of 127 cases found that 45% survived to be discharged, and median survival for discharged cats was 117 days (Smith *et al.*, 2003), although cats with congestive heart failure had a significantly shorter survival time than cats without this problem.

#### Spinal haemorrhage

Bleeding disorders can cause focal signs of myelopathy. For a full discussion see Chapter 14.

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# **Monoparesis**

## Sònia Añor

#### Introduction

The term monoparesis denotes the presence of neurological deficits in one limb. However, monoparetic animals are frequently presented to the veterinary surgeon with the main complaint being lameness. True paresis and lameness of orthopaedic origin can be difficult to differentiate so complete and careful neurological and orthopaedic examinations are mandatory. A lame dog or cat without an obvious orthopaedic cause may well have a neurological lesion which, in many cases, could be resolved if detected early in the course of the disease, whereas a delayed diagnosis (i.e. nerve root neoplasia) can have devastating consequences.

Figure 16.1 summarizes the definitions of the more commonly used clinical terms in this chapter.

## **Clinical signs**

The monoparetic animal shows motor dysfunction (usually manifested as weakness) in one limb and frequently sensory dysfunction (manifested as conscious proprioceptive deficits and areas of hypoaesthesia or anaesthesia) in the same limb.

Monoparesis is most commonly caused by dysfunction of the lower motor neurons (LMNs) innervating the affected limb (see Chapter 2). The lesion responsible for the dysfunction may affect the motor neuron cell body in the ventral horn of the spinal cord grey matter, its axon (ventral nerve root, spinal nerve, peripheral nerve) or the neuromuscular junction (see Chapter 2). A lesion affecting either a single nerve or several nerves that lie in close proximity (i.e. in the

brachial or lumbosacral plexi) can result in clinical monoparesis.

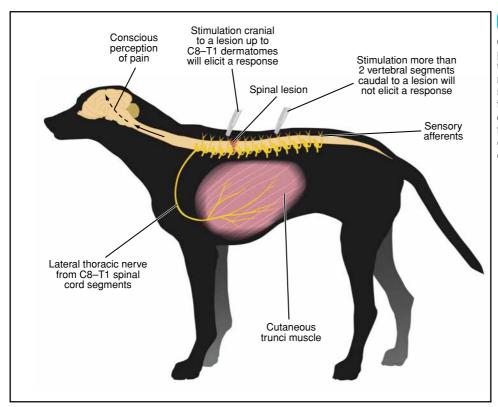
Thoracic limb monoparesis can present in conjunction with ipsilateral Horner's syndrome and/or a decrease or loss of the ipsilateral cutaneous trunci reflex (see Chapters 1 and 2).

- Horner's syndrome is caused by decrease or loss of sympathetic innervation to the eye. Lesions affecting the T1 and T2 ventral nerve roots can injure the preganglionic sympathetic nerves exiting the spinal canal at this level and cause miosis (partial Horner's syndrome) of the ipsilateral pupil (see Chapter 9). Complete Horner's syndrome (miosis, ptosis, enophthalmos, protrusion of the third eyelid) rarely occurs with lesions in this location.
- Decrease or loss of the ipsilateral cutaneous trunci reflex occurs when the C8–T1 motor neuron cell bodies or ventral nerve roots forming the lateral thoracic nerve are injured, thus causing subsequent decrease or loss of innervation of the ipsilateral cutaneous trunci muscle (Figure 16.2).

Lateralized disc protrusions or extrusions localized to the caudal cervical spine will commonly cause cervical pain in addition to motor dysfunction of one thoracic limb (monoparesis) or the ipsilateral thoracic and pelvic limbs (hemiparesis). Lateralized disc extrusions or protrusions localized to the caudal lumbar spine or lumbosacral junction can cause ipsilateral pelvic limb monoparesis with neurological deficits localizing to the L4–S2 nerve roots (femoral and sciatic nerves).

Clinical term	Definition
Monoparesis	Decreased voluntary motor function of one limb
Monoplegia	Absent voluntary motor function of one limb
Mononeuropathy	Dysfunction of a single peripheral nerve
Nerve root signature	Pain manifested as lameness due to nerve root irritation/compression
Horner's syndrome	Miosis, ptosis, enophthalmos and protrusion of the third eyelid
Paraesthesia	Abnormal sensation – tingling or itching – due to denervation, usually in the distal part of limbs. Can lead to self-mutilation

6.1 Definitions of clinical terms.



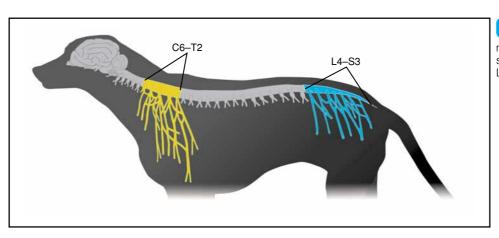
A schematic representation of the neurological pathways responsible for the cutaneous trunci reflex. Cutaneous stimulation along the thoracolumbar region will often elicit a twitching of the skin. The twitching is due to contraction of the cutaneous trunci muscle.

#### **Lesion localization**

Lesion localization for monoparesis is summarized in Figure 16.3. Lesions causing monoparesis of the thoracic limbs can commonly be located in the grey matter of spinal cord segments C6-T2, or at any anatomical region of the peripheral nerves forming the brachial plexus (Figure 16.4). Lesions affecting the spinal cord at this level can also cause ipsilateral hemiparesis if they affect the upper motor neurons (UMNs) to the ipsilateral pelvic limb. Unilateral spinal cord lesions (Figure 16.5) at C1-C5 will more commonly cause ipsilateral UMN hemiparesis. UMN monoparesis of the pelvic limbs can be caused by unilateral T3-L3 spinal cord lesions, whereas lesions causing LMN monoparesis of the pelvic limbs will be located in the L4-S2 spinal cord segments, or will affect the peripheral nerves of the lumbosacral plexus (Figure 16.6).

Ipsilateral partial Horner's syndrome and loss of the ipsilateral cutaneous trunci reflex indicate lesions affecting the C8–T2 spinal cord segments or their respective nerve roots.

In order to localize a lesion causing monoparesis accurately, it is important to know the motor and sensory innervation of the thoracic and pelvic limbs (Figures 16.7 and 16.8). The cutaneous area innervated by a particular nerve is called the dermatome or cutaneous zone of that nerve. This area includes a peripheral zone (where there is overlapping of several cutaneous zones) and a central autonomous zone innervated exclusively by that nerve (Bailey and Kitchell, 1987). Sensory dysfunction (decrease or loss of cutaneous sensation) in these specific autonomous zones can localize the lesion to one or more specific peripheral nerves or spinal cord segments (Figure 16.9).



Lesion localization for monoparesis; spinal cord segments C6–T2 and L4–S3 are highlighted.

Nerve	Spinal cord segments	Muscles innervated	Reflexes affected	Muscle function loss	Cutaneous sensation	Signs of dysfunction
Suprascapular	C6-C7	Supraspinatus; infraspinatus	-	Shoulder extension	Shoulder	Little/limited gait abnormality ± shoulder abduction
Musculocutaneous	C6-C8	Biceps brachii; brachialis	Biceps; withdrawal (flexor)	Elbow flexion	Medial antebrachium and first digit	Little/limited gait abnormality, weak elbow flexion
Radial	C7–T2	Triceps brachii; extensor carpi radialis; digital extensors	Triceps, extensor carpi radialis	Elbow extension; carpus extension; digit extension	Cranial antebrachium and foot	Loss of weight bearing, knuckling
Median and ulnar	C8-T2	Superficial and deep digital flexors; carpal flexors	Withdrawal (flexor)	Carpus flexion Digit flexion	Caudal antebrachium and foot, lateral aspect of 5 <sup>th</sup> digit	Little/limited gait abnormality; mild carpus hyperextension
Lateral thoracic	C8-T1	Cutaneous trunci	Cutaneous trunci	Cutaneous trunci	-	-
Sympathetic nerves to head and neck	T1–T3	Dilator of pupil	Pupillary light	Pupil dilation	-	Miosis (partial Horner's syndrome); ipsilateral peripheral vasodilation causing elevated skin temperature

16.4 Origins and functions of the peripheral nerves of the brachial plexus.

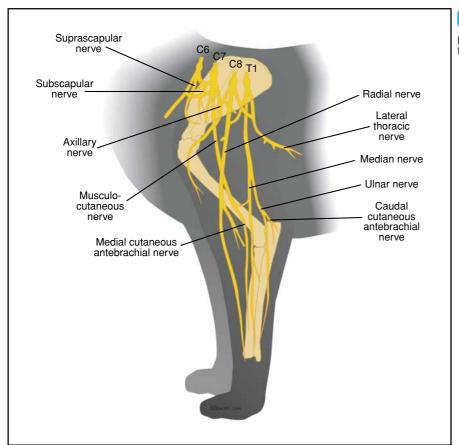
Spinal cord lesion localization	Signs in thoracic limbs	Signs in pelvic limbs	Other signs
C1-C5	UMN signs	UMN signs	
C6-T2	LMN signs	UMN signs	Horner's syndrome [9] Loss of ipsilateral cutaneous trunci reflex Possible self-mutilation of ipsilateral limb
T3-L3	Normal	UMN signs	
L4-S2	Normal	LMN signs	Incontinence [18] Flaccid tail Flaccid anus Possible self-mutilation of ipsilateral limb

Clinical signs caused by unilateral spinal cord lesions. (Numbers in square brackets denote the chapters where these are discussed in detail.)

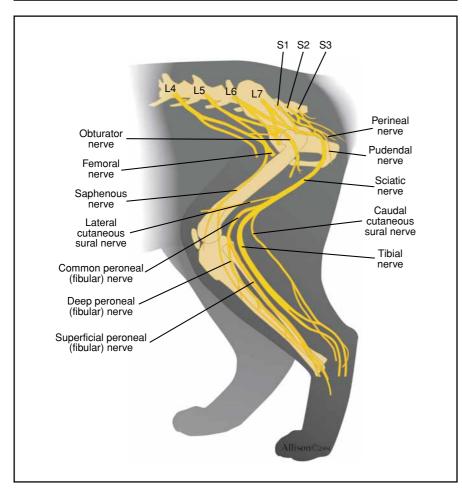
Nerve	Spinal cord segments	Muscles innervated	Reflexes affected	Muscle function loss	Cutaneous sensation	Signs of dysfunction
Obturator	L4–L6	Pectineus; gracilis	-	Hip adduction	-	Little/limited gait abnormality
Femoral	L4-L6	Quadriceps group; psoas group	Patellar	Stifle extension, hip flexion	Medial surface of limb and first digit	Loss of weight bearing
Sciatic	L6-S2	Biceps femoris; semimembranosus; semitendinosus; cranial tibial; gastrocnemius	Withdrawal (flexor); cranial tibial; gastrocnemius	Hip extension; stifle flexion; hock flexion and extension; digits flexion and extension	Entire limb, except medial aspect and first digit	Knuckling of paws but weight bearing present
Peroneal	L6-S2	Cranial tibial	Cranial tibial	Hock flexion digit extension	Craniolateral surface of limb, distal to stifle	Hyperextended hock; knuckled paw
Tibial	L6-S2	Gastrocnemius	Gastrocnemius	Hock extension; digit flexion	Caudal surface of limb, distal to stifle	Dropped hock

16.6 Origins and functions of the peripheral nerves of the lumbosacral plexus.

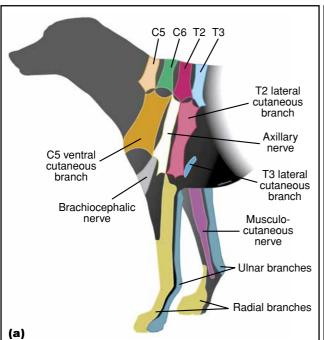
## Chapter 16 Monoparesis

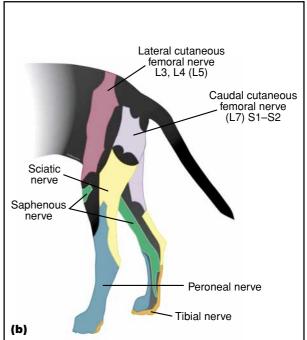


A schematic representation of the peripheral nerve supply to the thoracic limb.



16.8 A schematic representation of the peripheral nerve supply to the pelvic limb.





Schematic illustration of the cutaneous autonomous zones of innervation of (a) the thoracic limb and (b) the pelvic limb. (Based on Bailey and Kitchell, 1984 and 1987, respectively.)

## **Pathophysiology**

16.9

Peripheral nerve injuries can be classified based on the degree of injury and physical and functional integrity of the nerve trunk.

- Neurapraxia refers to interruption of nerve conduction without physical disruption of the axon. This type of injury is more commonly caused by transient loss of blood supply, blunt trauma or compression, which can sometimes cause demyelination without axonal discontinuity. Recovery is usually spontaneous and complete, and occurs within 1–2 weeks. If demyelination has occurred recovery may take a little longer (5–6 weeks).
- Axonotmesis refers to physical interruption of the axon, with separation of the axon from the neuronal cell body, which results in Wallerian-like degeneration and loss of conduction distal to the injury. The endoneurium and the Schwann sheath remain intact. Recovery, if possible, depends on the regrowth of axons, usually at 1 mm/day (Uchida et al., 1993).
- Neurotmesis implies complete severance of the nerve trunk (axons, Schwann cells and supporting connective tissue). This is the most severe type of injury. Successful regeneration to the correct target is unlikely to occur and may result in neuroma formation.

## **Differential diagnoses**

The main disease conditions causing acute non-progressive and chronic progressive monoparesis are listed in Figure 16.10.

#### Acute non-progressive

Trauma [16]:

Brachial plexus avulsion

Radial nerve injury

Sciatic nerve injury

Fibrocartilaginous embolic myelopathy [14, 15]

Arterial thromboembolism [15, 16]

## **Chronic progressive**

Foraminal stenosis:

Disc disease [14, 15, 16]

Neoplasia:

Nerve sheath tumours [16]

Spinal tumours [15]

Inflammatory disease:

Myelitis/meningomyelitis [10]

Plexus neuritis [16]

Peripheral neuropathy [14]

16.10 Differential diagnoses for clinical monoparesis. (Numbers in square brackets denote the chapters in which the subject is discussed in detail.)

## **Neurodiagnostic investigation**

All the specific diagnostic tests to assess a monoparetic animal need to be performed under general anaesthesia (see Chapter 20). A minimum database of complete blood count (CBC), serum biochemistry profile, urinalysis, thoracic radiographs and abdominal ultrasonography is indicated in any neurological patient. These tests are required to assess the general health status of the patient and rule out metastatic neoplasia or systemic disease. In addition, a comprehensive coagulation profile (activated clotting time (ACT), pro-

thrombin time (PT), activated partial thromboplastin time (aPTT), fibrin degradation products (FDPs)) should be performed when vascular (haemorrhage, infarction) disease is suspected.

## **Electrodiagnostic tests**

Electrodiagnostics provide more accurate information about the integrity and function of peripheral nerves (see Chapter 4).

Electromyography (EMG) allows detection of spontaneous electrical activity (fibrillation potentials and positive sharp waves) in denervated muscles 7–10 days after the nerve injury has occurred. If regeneration is producing reinnervation, this can be detected by the presence of giant motor unit potentials on EMG, so repeated studies to monitor progress after acute injuries are useful.

Motor and sensory nerve conduction velocity studies (MNCV, SNCV) can be performed in specific peripheral nerves to assess nerve function and integrity, and to determine the severity of the lesion.

Cord dorsum potentials can also be recorded to assess dorsal nerve root function in cases of sensory nerve dysfunction (Cuddon *et al.*, 1999)

F wave studies allow assessment of ventral nerve root function in cases of proximal motor nerve injuries.

## **Imaging**

#### Radiography

Survey radiographs of the vertebral column may show signs of intervertebral disc disease, enlarged intervertebral foramina in cases of peripheral nerve sheath tumours, or lytic changes indicative of other neoplasms.

## Myelography

A myelogram can be helpful in cases of lateralized intervertebral disc extrusions and protrusions, as well as in cases of peripheral neoplasms that grow into the vertebral canal.

## Computed tomography and magnetic resonance imaging

CT and MR imaging techniques can be useful additional diagnostic tests to detect and better determine lateralization and extension of nerve root tumours, intervertebral disc disease, fibrocartilaginous embolism and other inflammatory or neoplastic conditions affecting the spinal cord.

## **Diseases causing monoparesis**

## **Degenerative diseases**

## Foraminal stenosis

Stenosis of intervertebral foramina is most commonly caused by lateralized disc protrusions or extrusions. However, any mass growing inside the intervertebral foramen (e.g. neoplasm, degenerative connective tissue) can also cause narrowing of the intervertebral foramina.

If foraminal stenosis occurs at the C6–T2 or L4–S2 vertebral levels, compression of brachial or lumbosacral plexus nerve roots can occur, causing subsequent monoparesis of the thoracic or pelvic limb, respectively.

**Clinical signs:** Animals with foraminal stenosis of the caudal cervical (vertebral level C5–C7), caudal lumbar (vertebral level L5–L7) or lumbosacral intervertebral foramina will show LMN signs localizing to one or more nerve roots.

Sensory signs, such as conscious proprioception deficits and areas of hypoaesthesia in the cutaneous areas of the affected nerve roots, can also be seen but they are not common and are difficult to assess.

The caudal cervical and lumbosacral vertebral column are the most mobile parts of the vertebral column. 'Nerve root signature' or pain, upon manipulation or palpation of the affected limb, is commonly found when there is nerve root impingement secondary to foraminal stenosis, and excessive vertebral movement causes intermittent compression of the affected nerve root. Lameness of the affected limb due to irritation or compression of the nerve root is also frequent. The animal may hold the affected limb in flexion, close to the body wall and not bear weight on it (see Chapter 13). This clinical sign may be constant, intermittent or exacerbated by exercise. The exacerbation of clinical signs during exercise described as 'neurogenic intermittent claudication' (Lenehan et al., 1998) is believed to be caused by engorgement of nerve root (radicular) blood vessels, causing further compression and ischaemia of the nerve root in an already narrowed foramen (Jones et al., 1996).

The most common site of foraminal stenosis is at the lumbosacral intervertebral foramen. Dogs with degenerative lumbosacral stenosis can develop stenosis (uni- or bilateral) of the lumbosacral foramina due to degenerative changes, and subsequent compression of the L7 nerve root. These animals may show pelvic limb monoparesis or lameness as the only clinical sign (Figure 16.11) Other animals present with clinical signs indicative of sciatic nerve involvement (i.e. pelvic limb paresis, atrophy of flexor muscles,



Paresis in the right pelvic limb of a German Shepherd Dog due to ipsilateral lumbosacral foraminal stenosis. (Courtesy of S. Platt)

pelvic limb conscious proprioceptive (CP) deficits). Most affected dogs exhibit severe pain on manipulation of the lumbosacral joint or extension of the coxofemoral joint.

Foraminal stenosis affecting the caudal cervical area may cause ipsilateral thoracic limb monoparesis. Cervical foraminal stenosis is most commonly caused by lateralized disc extrusions/protrusions. Other less frequent causes include formation of synovial cysts at the articular processes (see Chapter 14) (Levitski et al., 1999; Dickinson et al., 2001) or any other kind of mass (i.e. neoplasm) growing inside the intervertebral foramina

Animals with caudal cervical foraminal stenosis may also show 'nerve root signature' signs manifested as pain on manipulation of the thoracic limb, lameness or voluntary flexion and non-weight bearing of the affected limb. Atrophy of the infraspinatus and supraspinatus muscles, detected clinically as a prominent scapular spine, can also be seen when the suprascapular nerve roots (C6–C7) are affected.

**Diagnosis:** Plain radiographs of the vertebral column may show the presence of calcified disc material inside the intervertebral foramen in cases of lateralized disc extrusions, but are often unremarkable. Soft tissue opacities inside the vertebral foramen may also be seen. Oblique plain radiographs of the cervical and lumbar spine allow better visualization of the intervertebral foramina and detection of any soft tissue or calcified mass in this location. Enlargement of the affected intervertebral foramen may also be observed.

Degenerative changes of the affected vertebrae in cases of lumbosacral degenerative stenosis or cervical stenosis may also be seen. These include:

- Enlarged articular facets
- Increased density of articular facets
- Spondylosis deformans
- Endplate sclerosis.

Myelography may be useful in identifying disc material, degenerative soft tissue or neoplastic tissue growing inside the intervertebral foramen and extending into the vertebral canal. However, results are normal if there is no encroachment into the canal.

CT and MRI are the most useful diagnostic tools to identify intervertebral foraminal stenosis (Figure 16.12). Transverse sections at the level of the affected intervertebral foramina will identify any kind of mass caus-



## 16.12

Transverse CT scan showing a foraminal disc extrusion at the C6–C7 right intervertebral foramen. (Courtesy of Dr Karen Vernau)

ing narrowing of the intervertebral foramen and nerve root entrapment. The abnormalities observed may be subtle, so careful assessment of transverse CT or MRI images, paying careful attention to any asymmetry (muscle mass, nerve root size, intervertebral foramen diameter) is essential.

Electromyography may demonstrate presence of spontaneous electrical activity in the muscles innervated by the affected nerve root, thus confirming the neurological origin of the deficits and differentiating this from orthopaedic disease.

**Treatment and prognosis:** Medical treatment with anti-inflammatory drugs (steroidal and non-steroidal) may help alleviate signs of radicular pain temporarily. However, pain and paresis usually relapse upon discontinuation of therapy. If anti-inflammatory therapy does not work, acupuncture can provide temporary pain relief.

Surgical removal of the extruded disc material or degenerative connective tissue causing narrowing of the intervertebral foramen is the only effective treatment. Dorsal laminectomy plus foraminotomy are indicated in cases of lumbosacral foraminal stenosis to relieve compression of the affected nerve root (see Chapter 21). In the cervical region, dorsal laminectomy plus facetectomy should be performed to remove lateralized disc extrusions or articular synovial cysts (see Chapter 21). If there are signs of vertebral instability (dynamic lesions), cervical or lumbosacral distraction and fusion techniques should be used to stabilize the affected vertebral segment and to avoid further progression of clinical signs (see Chapter 21).

Surgical removal of disc material or connective tissue from the intervertebral foramen is a difficult task and requires specialized neurosurgical skills. When nerve root decompression is not complete, radicular pain and lameness or paresis may persist. Thus the prognosis depends on the ability to relieve the compression in addition to the degree of damage to the nerve root(s).

## **Anomalous diseases**

## Peripheral neuropathy

Peripheral nerve diseases can occasionally cause monoparesis if they affect a single nerve or the nerves of the brachial or lumbosacral plexuses. However, peripheral neuropathies more commonly affect more than one limb and are discussed further in Chapter 14.

## **Neoplastic diseases**

## Nerve sheath tumours

Peripheral nerve tumours represent approximately 27% of all canine nervous system tumours (Hayes *et al.*, 1975). Tumours of nerve sheath origin arise from cells surrounding the axons in peripheral nerves or nerve roots. In the past, these tumours were classified as:

- Neurinomas
- Neurilemmomas
- · Neurofibromas

- Neurofibrosarcomas
- Schwannomas
- Malignant schwannomas.

Most peripheral nerve sheath tumours (PNSTs) in dogs are anaplastic with a high mitotic index and an aggressive biological behaviour, so they are now designated as malignant peripheral nerve sheath tumours.

Malignant PNSTs in dogs most commonly affect the caudal cervical (C6-C8) and the cranial thoracic (T1-T2) nerve roots (Carmichael and Griffiths, 1981; Brehm et al., 1995). These tumours may have their origin in the nerve roots, the brachial or lumbosacral plexi, or they may arise from more peripheral locations in the nerves. Usually, the tumour spreads slowly, both distally and proximally, and may invade the vertebral canal causing spinal cord compression and associated neurological deficits. As the tumours grow proximally they spread to neighbouring nerves in the plexus bundle, with a high percentage of dogs showing evidence of multiple nerve involvement at the time of diagnosis. PNSTs are highly invasive locally, but they rarely metastasize, although pulmonary metastasis in advanced cases has been described (Carmichael and Griffiths, 1981; Bradley et al., 1982).

Clinical signs: Slowly progressive thoracic limb lameness or paresis, and muscle atrophy are the predominant clinical signs of malignant PNSTs. In addition pain upon palpation of the limb or axillar region may be encountered. A palpable axillar mass may be present in some cases, but it is not common. Clinical signs progress slowly and orthopaedic disease is often suspected before a definitive diagnosis is made. As the peripheral nerve sheath tumour spreads proximally and compresses the spinal cord, neurological deficits may develop in the ipsilateral pelvic limb progressing to all four limbs. If the dorsal cervical nerve roots are affected, animals may also show cervical pain.

Unilateral, partial or complete Horner's syndrome may appear if the cranial thoracic nerve roots are affected by the tumour itself or if there is cord compression at this point. Similarly, the ipsilateral cutaneous trunci reflex may be absent due to invasion of the C8—T1 ventral nerve roots or compression of these spinal cord segments.

No sex or breed predilection has been demonstrated for PNSTs in dogs. Most affected animals are adults over 7 years of age, but younger and older animals may also be affected.

**Diagnosis:** Orthopaedic disease must be excluded by careful orthopaedic examination and radiographs of the thoracic limb joints. Complete bloodwork (CBC, serum biochemistry panel), thoracic radiographs and abdominal ultrasonography should be performed in any dog suspected of having a malignant PNST to rule out metastatic disease and assess general health status.

Survey radiographs of the spine are often normal. Oblique views may reveal enlargement of the affected intervertebral foramen due to pressure atrophy, caused by the thickened nerve root. Occasionally, lysis of the

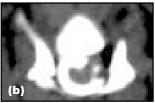
affected vertebral bodies may be observed.

Myelography may be useful to detect spinal cord or nerve root compression once the tumour has reached this location. An intradural—extramedullary defect may be seen at the point where the nerve root exits from the spinal cord (Figure 16.13a).

CT imaging allows visualization of some malignant PNSTs (Figure 16.13b), but it is not very sensitive, particularly early in the course of the disease. Enhancement of the mass with iodinated contrast medium provides excellent views. Contrast enhancement helps differentiate vascular structures and allows subtle differences in soft tissue opacity created by tumour vasculature to be seen (Niles *et al.*, 2001).



Nerve root neoplasia.
(a) Ventrodorsal
myelogram showing an
intradural–extramedullary
lesion at the C6–C7 intervertebral foramen (arrowed).
(b) Transverse CT scan showing
enlargement of the ventral and
dorsal nerve roots at this level.



MRI evaluation of the brachial plexus or peripheral nerves provides excellent diagnostic images but again, not all PNSTs can be detected using this imaging modality early in the course of the disease. On MR images, PNSTs are usually hyperintense on T2-weighted images and isointense to surrounding soft tissue structures on T1-weighted images. Contrast enhancement with paramagnetic contrast media may allow precise delineation of the tumour mass and detection of vertebral canal invasion (Platt *et al.*, 1999) (Figure 16.14).

Electromyography reveals abnormal, spontaneous electrical activity in the affected limb muscles and is of great assistance in differentiating neurological from orthopaedic disease (see Chapter 4).



MRI image 16.14 (T1weighted, after intravenous contrast administration, dorsal view) of a peripheral nerve sheath tumour arising from the C2 nerve root. Note extension of the neoplasm inside the vertebral canal. causing secondary spinal cord compression.

**Treatment and prognosis:** Unfortunately, there is usually no curative treatment for PNSTs. Complete surgical resection may be difficult due to the invasive behaviour of these tumours and the late detection of the disease in most cases.

Tumours within the brachial plexus or peripheral nerves are treated with local excision or amputation of the affected limb. Tumours located within the spinal canal necessitate a dorsal laminectomy or hemilaminectomy to be resected. Tumours originating in the spinal canal and extending peripherally or originating in the plexus and extending proximally can be approached both peripherally and through a laminectomy, and often necessitate a durotomy and rhizotomy (nerve root resection). Repeated surgeries may be needed as recurrences are common. In many instances, amputation of the limb is the only option. Surgery can be followed by a course of radiation therapy, but it is unclear whether this positively affects the prognosis.

Despite aggressive management, the overall prognosis is considered poor for most cases of malignant PNSTs. Recurrence rate after surgery is high.

In one report, there was a tendency for dogs with more proximally located tumours to respond more poorly to surgery and to relapse earlier (1 month for nerve root tumours and 7.5 months for plexus tumours) than those with peripherally located tumours (>9 months after surgery) (Brehm *et al.*, 1995). Incomplete resection is common, indicating that grossly visible margins at the time of surgery are frequently inaccurate indicators of tumour excision.

Early diagnosis and aggressive surgical intervention are recommended to maximise the possibility of complete tumour resection. Aggressive surgical resection at an early stage, if the tumour is peripheral, can be curative.

## Other neoplastic diseases

Any neoplastic condition of the spine, meninges or spinal cord can cause monoparesis of a pelvic limb if located laterally within the vertebral canal caudal to the third thoracic spinal cord segment. Meningiomas in particular can cause initial signs that are lateralized. However, most spinal tumours cause bilateral disease. Rare examples of tumours that can affect a peripheral nerve or plexus causing monoparesis are listed below.

Lymphoma: Lymphoma is the most common tumour that affects the spinal cord in cats. Affected cats are usually young (<5 years old) and are infected with the feline leukaemia virus. Typically there is an extradural mass causing spinal cord compression and signs of myelopathy. However, there are several reports of spinal lymphoma in which there was infiltration of the brachial plexus in cats causing initial signs of monoparesis (Fox and Gutnick, 1972; Spodnik et al., 1992). This disease is described in full in Chapter 15.

**Others:** Whenever a tumour grows adjacent to a nerve, it can cause compression of that nerve. Examples of tumours that can behave in this way include:

- Vertebral tumours (see Chapter 15)
- Infiltrating liposarcomas and other sarcomas
- Ganglioneuromas
- Malignant apocrine sweat gland (one reported case; Carmichael and Griffiths, 1981).

Clinical presentation mimics that of a peripheral nerve sheath tumour but a mass may be palpable and should be identifiable on CT or MRI.

## Inflammatory diseases

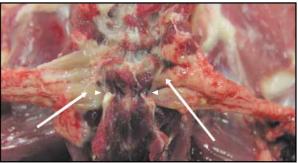
#### Myelitis/meningomyelitis

Focal forms of myelitis and meningomyelitis of infectious or immune-mediated origin can cause monoparesis of the thoracic or pelvic limbs when the inflammatory focus is unilateral and located in the brachial (C6–T2) or lumbosacral (L4–S2) intumescences of the spinal cord. These diseases are described and discussed in detail in Chapter 10.

#### Plexus neuritis

This is an uncommon inflammatory condition that can affect the brachial plexus of dogs (Cummings *et al.*, 1973; Alexander *et al.*, 1974) and cats (Bright *et al.*, 1978) (Figure 16.15). Reported cases describe an acute onset of thoracic limb paresis with decreased or absent spinal reflexes. A similar condition in humans (serum neuritis) has been described after the administration of certain vaccines (Miller *et al.*, 2000) and associated with specific viral infections (Fabian *et al.*, 1997). The pathogenic mechanism is believed to have an immunoallergic basis that causes severe shoulder and upper arm pain followed by upper arm weakness.

The sporadic cases described in dogs and cats have been related to a purely horsemeat diet (one dog) and to administration of modified-live rabies virus vaccines (one dog, one cat). In other animals a definite cause could not be found. Affected animals show diffuse EMG changes consistent with denervation in the thoracic limbs and neurogenic atrophy in all thoracic limb muscles. Cerebrospinal fluid (CSF) evaluation is usually normal. Pathological examination shows severe Wallerian degeneration of the brachial plexus nerves, most pronounced in the ventral nerve roots, together with a prominent inflammatory infiltration of



Brachial plexus neuritis with bilateral nerve root swelling in a 9-year-old Burmese cat. This postmortem specimen shows the swollen nerves (arrowed) as they exit ventrally from the intervertebral foramina (arrowheads). (Courtesy of Tim Scase and Laurent Garosi)

mononuclear cells. Affected dogs may respond to corticosteroid treatment and/or a change to a poultry-based diet that contains no beef or horse products. Prognosis is guarded, since some animals may recover slowly (months) while others may remain non-ambulatory. The single feline case reported recovered spontaneously over a 3-week period.

#### **Traumatic diseases**

#### **Brachial plexus avulsion**

Traumatic injuries causing avulsion of the nerve roots of the brachial plexus are the most common cause of acute thoracic limb monoparesis or monoplegia in small animals. They are usually caused by road traffic accidents or falls from a height, as a result of abduction and simultaneous caudal displacement of the thoracic limbs.

The site of root avulsion is usually intradural where the nerve roots arise from the spinal cord. At this point, nerve roots lack a well defined perineurium and constitute the weakest structure between the spinal cord and the peripheral nervous system. If the avulsion is severe enough, it may place traction over the spinal cord and damage spinal cord pathways, causing ipsilateral pelvic limb neurological deficits. Both dorsal and ventral nerve roots can be affected, but the motor roots appear to be more susceptible to this type of trauma (Griffiths, 1974)

**Clinical signs:** Signs are peracute in onset following the traumatic incident. Depending on which nerve roots are affected, avulsions are divided into three types:

- Cranial avulsions (C6–C7 nerve roots)
- Caudal avulsions (C8–T2 nerve roots)
- Complete avulsions (C6–T2 nerve roots).

Cranial avulsions are rare and result in few clinical signs. The elbow extensor muscles are not affected, so the animal can bear weight on the affected limb. There is loss of shoulder movement and elbow flexion, and atrophy of supraspinatus and infraspinatus muscles usually develops.

Caudal and complete avulsions are more common and cause more severe clinical signs (Griffiths *et al.*, 1974). They both cause paralysis of the triceps brachii muscle, so the animal cannot extend the elbow or bear weight on the affected limb. Affected animals drag the limb knuckled over (Figures 16.16 and 16.17). Thoracic limb muscles are hypotonic and severe neurogenic atrophy starts about one week after the injury. Spinal reflexes and postural reactions are lost. If the elbow flexor muscles are spared (caudal avulsions) the animal can carry the limb flexed at this level, avoiding contact with the floor.

Sensory signs are also common. The pattern of decreased or absent sensation in the affected limb allows better determination of the type of avulsion (Figure 16.18) (Bailey and Kitchell, 1987). Cutaneous sensation should be checked in the entire limb, but particular attention should be paid to deep pain sensa-





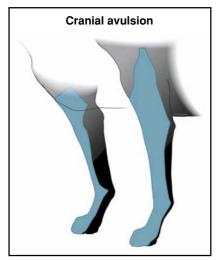
avulsion caused by a road traffic accident in a 3-year-old male Mastiff. Note that only one limb is affected. The close up of the affected limb demonstrates severe neurogenic atrophy.



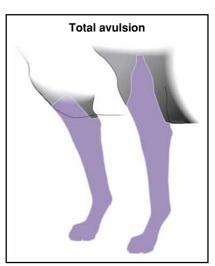
Brachial plexus avulsion. Excoriations are seen in the affected thoracic limb, secondary to dragging of the limb and decreased sensation.

tion in the denial (radial and musculo-cutaneous) and lateral (radial and ulnar) digits, since it is essential in determining a prognosis.

A high percentage of patients with brachial plexus avulsions show partial Horner's syndrome and/or loss of cutaneous trunci reflex ipsilateral to the side of the avulsion (Wheeler *et al.*, 1986). Avulsion of the T1 ventral nerve root causes injury to the pre-ganglionic sympathetic nerve fibres to the eye, causing ipsilateral miosis (partial Horner's syndrome). Loss of the cutaneous trunci reflex is caused by damage to the C8–T1







Sensory loss associated with brachial plexus avulsion. Shaded zones are dermatomes that lack sensation. (Based on Bailey, 1984)

ventral spinal nerve roots that form the lateral thoracic nerve and innervate the cutaneous trunci muscle. The contralateral reflex is usually present after ipsilateral stimulation.

**Diagnosis:** A history of thoracic limb monoparesis after a traumatic incident should raise a high suspicion of brachial plexus avulsion. Every animal unable to use one thoracic limb after trauma should be examined carefully to detect orthopaedic as well as neurological abnormalities.

MRI of the affected plexus may provide information on the degree of nerve and associated soft tissue trauma.

Electromyography allows detection of spontaneous electrical activity in the denervated muscles 7–10 days after the injury (Steinberg, 1979). Nerve conduction velocity studies of the radial and ulnar nerves allow determination of the degree of injury (see Chapter 4). Since the radial nerve is commonly injured in brachial plexus avulsions, serial electrodiagnostic evaluations of this nerve may provide useful diagnostic and prognostic information. Early decreased radial nerve conduction velocity indicates a poor prognosis (Faissler *et al.*, 2002).

**Treatment:** Unfortunately, there is no routinely effective treatment for this type of injury. The degree of recovery depends only on the severity of the nerve lesion at the time of injury.

- If deep pain is present in the medial and lateral digits, prognosis for recovery is good and aggressive physiotherapy should be recommended to the owner (see Chapter 24).
- If deep pain sensation is absent, prognosis will depend on the severity of axonal injury, being good for neurapraxic lesions, but guarded to poor for axonotmetic and neurotmetic lesions. Pure axonotmesis occurs rarely, so potential for recovery, although present, is low and prognosis poor.

When the proximal branches of the radial and musculocutaneous nerves are spared – so that the elbow flexor and extensor muscles are not denervated – corrective surgery can be used to provide carpal extension and prevent the distal part of the limb from collapsing (Steinberg, 1988). Tendon transplantation or carpal arthrodesis procedures can be performed.

- Muscle tendon transplantation can be successful in partial avulsions.
- Carpal fusion can be useful in animals with adequate triceps function that walk knuckling over on their carpus (Steinberg, 1988).

Before performing any type of surgery, it is essential to perform EMG to determine that elbow extensors or the muscles to be transplanted have normal function and are not denervated. However, amputation may be necessary if sensation is lost and excoriations and self-mutilations secondary to paresthesias develop. The reader is referred to standard surgical texts for further information on these surgical procedures.

Finally, experimental studies in dogs demonstrate that ventral root reimplantation can promote successful reinnervation (Moissonnier *et al.*, 1998, 2001). Supportive treatment is essential during the recovery time to prevent contractures and excoriations from dragging the limb. Keeping the limb clean and dry, treating any wounds that may develop, covering the foot with boots or bandages are all important therapeutic measures. At the same time, performing physical therapy (flexion and extension movements) several times a day is crucial to lessen muscle atrophy as well as to prevent muscle contractures and joint fusions (see Chapter 24).

**Prognosis:** Outcome is often good for animals with cranial plexus avulsions that are able to bear weight on the affected limb and maintain normal sensation over the distal part of the limb.

Animals with caudal and complete brachial plexus avulsions have a poor to guarded prognosis if

neurotmesis has occurred. Only those with neurapraxic injuries show improvement and recover completely. However, most animals do not improve but go on to show severe limb atrophy, eventually developing serious complications such as: trophic ulcers; joint contractures or self-mutilations from paraesthesias; or abnormal sensation in the affected areas produced by regeneration of sensory nerves (Sharp, 1995). In these cases, amputation of the limb is necessary.

Decreased radial nerve conduction velocity at the beginning of clinical signs is a poor prognostic indicator (Faissler *et al.*, 2002). If the situation remains unchanged after 4 weeks, with concurrent severe EMG changes in the triceps, there is virtually no chance of spontaneous recovery. However, the presence of giant motor unit potentials in any of the affected muscles is an indicator of reinnervation (Griffiths and Duncan, 1978) and may represent a favourable prognostic sign.

The best predictor of complete recovery seems to be pain perception (Faissler *et al.*, 2002). Preservation of pain sensation is an indicator of a milder type of injury and should prompt the clinician to recommend supportive therapy while waiting for motor function to recover. However, if no improvement is seen during the first 2 months, recovery is unlikely to occur.

#### Radial nerve injury

The radial nerve can be injured proximally by fractures of the first rib or distally by humeral fractures. Fractures of the humerus can cause radial nerve injury at sites proximal and distal to the branches that supply the triceps muscle.

- If the lesion is *proximal* to these branches, the elbow, carpal and digital joints cannot extend, so the elbow is 'dropped' and the animal walks with the carpus and digits knuckled over.
- If the lesion is distal to these branches the animal can extend the elbow, but the carpus still knuckles over when the animal walks due to paralysis of the carpal and digital extensor muscles.

Unless there is complete section of the nerve, most animals recover completely within a few months. However, if neurotmesis has occurred, cutaneous sensation is lost in the cranial aspect of the limb distal to the injury and deep pain sensation is absent in the lateral digit. In these cases, prognosis for recovery is poor. In addition, development of paraesthesias may lead to self-mutilation.

## Lumbosacral plexus trauma

Traumatic injuries to the lumbosacral plexus resulting in pelvic limb monoparesis most often affect the sciatic trunk or nerve.

#### Caudal lumbar trauma – lumbosacral trauma

The sciatic nerve originates from spinal cord segments L6—S2. These segments lie cranially inside the vertebral canal, approximately over the L4—L5 vertebral bodies (see Chapter 2). After exiting from the spinal cord, the nerve roots forming the sciatic nerve run

caudally in the vertebral canal until their exit through the corresponding intervertebral foramina. Within the vertebral canal, nerve fibres forming the sciatic nerve can be injured by any trauma (e.g. fractures, luxations) affecting the caudal lumbar vertebrae or lumbosacral junction. However, traumatic lesions affecting this area will more often affect the nerve roots forming the pudendal, pelvic and caudal nerves, which run inside the vertebral canal together with the sciatic nerve fibres at this level. Thus, most injuries to this area will not cause a true monoparesis, and neurological deficits related to dysfunction of these other nerves will be present (see Chapter 18). In addition, most vertebral injuries will cause bilateral deficits. Foraminal stenosis of the lumbosacral junction secondary to degenerative lumbosacral stenosis may cause a true sciatic monoparesis (see above).

#### Pelvic trauma

Traumatic injuries to the pelvic area causing fractures of the shaft of the ilium or acetabulum or sacroiliac fracture/luxation are common causes of proximal sciatic nerve injury or injury to the lumbosacral plexus. For a more complete discussion on the classifications and specific management of sacral and pelvic fractures, the reader is referred to standard surgical texts and the BSAVA Manual of Small Animal Fracture Repair and Management.

Proximal sciatic nerve dysfunction causes severe pelvic limb monoparesis. The affected animal should be able to bear weight on the affected limb, but will walk with the paw knuckled over, the stifle joint will not flex, and the tarsus and digits will not flex or extend. In addition the hock is usually 'dropped'. Sensation is affected in the entire limb except for the medial aspect. which is supplied by the saphenous branch of the femoral nerve. The flexor reflex is severely affected due to inability of the patient to flex its stifle, hock or digits. If the medial digit is stimulated a mild flexion of the hip (femoral nerve) can be observed. Deep pain sensation should be checked in all digits to assess severity of the lesion. The sciatic nerve supplies sensation to all digits in the pelvic limbs, except the medial one, which is innervated by the saphenous branch of the femoral nerve. Lack of deep pain sensation in the digits innervated by the sciatic nerve indicates severe injury (neurotmesis) and a poor prognosis for recovery.

Pelvic fractures cause compression or laceration of the sciatic nerve or lumbosacral plexus. Surgical exploration and decompression of the nerve plus internal fixation is indicated if the animal shows moderate to severe signs of peripheral nerve injury (deep pain sensation preserved) and severe pain, to relieve nerve entrapment, avoid further damage by unstable fractures and assess prognosis (Jacobson and Schrader, 1987). If no improvement is seen in 3–4 months, prognosis is poor and amputation of the limb is recommended to avoid excoriations and self-mutilation.

#### Proximal sciatic nerve injuries

The proximal segment of the sciatic nerve is often injured by entrapment caused by muscle or fibrous tissue that can develop secondary to:

- Femoral fractures
- · Ischial fractures
- Acetabular fractures
- Femoral head and neck excision surgical procedures
- Triple pelvic osteotomy
- · Surgery of the coxofemoral joint
- · Intramuscular injections
- Pinning of the femur.

The more common injuries result from retrograde intramedullary pinning of the femur (Fanton *et al.*, 1983), from ischial and acetabular fractures (Chambers and Hardie, 1986) or from intramuscular injections of various agents into the caudal thigh.

Retrograde intramedullary pinning of the femur may injure the sciatic nerve directly from pin insertion or secondarily by scar formation around the nerve due to excessive pin length. Acetabular or ischial fractures can damage the sciatic nerve directly or by entrapment secondary to progressive fibrosis at the fracture site. Intramuscular injections in the caudal thigh may cause direct laceration of the sciatic nerve by needle placement, injection of the substance into the nerve, or secondary injury due to scar formation around the nerve. The degree of nerve damage varies with the agent injected (penicillin, diazepam, chlorpromazine and some steroids, especially hydrocortisone and triamcinolone acetonide cause severe damage), the amount of drug injected and the site of injection (intrafascicular injections cause more severe damage than extrafascicular injections). To avoid this type of injury, intramuscular injections should be given in other muscle groups, such as the quadriceps or lumbar muscles.

Prognosis for this type of injury depends on the severity of nerve damage, with loss of deep pain sensation in the digits innervated by the sciatic nerve indicating a poor prognosis. If deep pain sensation is preserved, early fixation of fractures, nerve decompression and aggressive physical therapy should be instituted to avoid further nerve damage and promote recovery of nerve and muscle function.

#### Peroneal and tibial nerve injuries

The peroneal nerve is exposed to traumatic injuries as it crosses the lateral aspect of the stifle. The more common causes of injury at this site include intramus-



16.19 Sciatic nerve dysfunction in a young male Siberian Husky. There were severe conscious proprioception deficits with loss of tone in the distal limb.

cular injections, pressure from orthopaedic casts and surgery of the stifle joint (cruciate ligament repair).

Isolated tibial nerve lesions are rare, but may occur following intramuscular injections into the thigh muscles. In most animals, tibial nerve lesions occur in association with peroneal or higher (main trunk) sciatic injuries. Pure peroneal or tibial nerve signs (Figure 16.19) are not common.

## Femoral nerve injuries

The spinal cord segments L4–L6 and femoral nerve roots within the vertebral canal can be affected by several disease conditions (disc disease, trauma, neoplasia). In these cases, bilateral disease is more common; true femoral monoparesis is a rare occurrence.

Peripheral femoral nerve injuries are not common because the nerve itself and its roots are well protected by the sublumbar musculature. However, extreme extension of the hip causing iliopsoas muscle tears can damage the femoral nerve and cause a femoral neuropathy. Other lesions occurring within this muscle group (neoplasms, haematomas) can also injure the femoral nerve fibres that run within the psoas muscle group after they exit the spinal canal.

*Clinical signs:* Dysfunction of the femoral nerve causes monoparesis with severe gait abnormalities. The patient cannot bear weight on the affected limb and carries it flexed at the stifle (Figure 16.20). There is little hip flexion and the patellar reflex is severely



Femoral nerve dysfunction in a 9-year-old male mixed breed dog. The inability to bear weight is profound, with the affected limb carried flexed at the stifle.

decreased or lost. Neurogenic atrophy of the quadriceps muscle usually develops. In severe lesions there is anaesthesia over the medial aspect of the pelvic limb and medial digit. Deep pain sensation should be checked in the medial digit to assess the severity of the injury.

**Diagnosis:** The diagnosis of traumatic peripheral neuropathies is based on history and clinical signs.

Electromyography helps to determine which muscles are affected, differentiating proximal lumbosacral injuries caused by pelvic trauma, from proximal sciatic nerve injuries. Nerve integrity may be assessed by

nerve conduction studies, stimulating proximal and distal to the site of injury.

**Treatment and prognosis:** This involves supportive measures to protect the foot from injuries, such as the use of boots or bandages, and physical therapy to preserve joint motion and delay muscle atrophy. Exploratory surgery to evaluate nerve damage and performing neurorrhaphy (anastomosis) or neurolysis (debriding inflammatory adhesions from the affected nerve) is indicated when there is severe nerve damage.

The prognosis is guarded in peripheral nerve injuries. Axonotmetic and neurapraxic lesions have a better prognosis than neurotmetic lesions. If pain perception is present there is a chance of recovery. Neurapraxic lesions recover in days to weeks, depending on the severity of the initial injury. In axonotmetic lesions, regrowth of axons occurs at 1–4 mm per day. However, after 6 months shrinkage of the nerve sheath may impede further growth. So, the closer the nerve injury is to the muscle to be reinnervated, the better the prognosis.

Serial EMG and nerve conduction velocity (NCV) examinations of the affected limb will help in determining prognosis. If these tests are not available, serial neurological examinations should be performed monthly for at least four months. If no improvement is seen in 4–6 months, recovery is unlikely and amputation of the affected limb should be considered.

#### **Toxic diseases**

#### **Tetanus**

Tetanus usually causes generalized signs of increased extensor rigidity and is described in full in Chapter 14. However, signs can be limited to a single limb, causing monoparesis associated with extensor rigidity. A wound can usually be found on the distal extremity of the affected limb. This syndrome has been reported in people and occurs either when the patient has preexisting anti-tetanus antibodies, or an extremely small injury. Local tetanus has been reported most commonly in cats but can occur in dogs (Malik *et al.*, 1989; Polizopoulou *et al.*, 2002).

## Vascular diseases

## Fibrocartilaginous embolism

Unilateral infarctions affecting the spinal cord ventral grey matter at the C6–T2 or the L4–S2 spinal cord segments, or affecting the white matter of the T3–L3 spinal cord segment may cause acute monoparesis of the thoracic (C6–T2) or pelvic limbs (T3–L3 and L4–S2). The paretic pelvic limb will show UMN deficits if the infarct occurs in the T3–L3 segment, and LMN deficits if the infarct occurs in the L4–S2 spinal cord segment.

Specific clinical signs, diagnosis, treatment and prognosis of this type of injury are discussed in detail in Chapter 15.

#### Arterial thromboembolism

The acute onset of monoparesis (thoracic or pelvic limbs) in cats can be associated with arterial thrombo-

embolism. The long-term prognosis is very poor as many cats have a severe underlying cardiovascular disease. Further details on this condition can be found in Chapter 15.

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# **Exercise intolerance, collapse and paroxysmal disorders**

Simon R. Platt and G. Diane Shelton

# Introduction

Exercise intolerance, which may also be considered as episodic weakness, occurs with activity and dissipates with rest. It is recognized as early fatigue with mild exercise, though in some cases more vigorous or prolonged exercise may be needed to induce the problem. It may be associated with episodic muscle cramps (prolonged, involuntary, painful muscle contractions).

Collapse of an acute nature may be one of three major forms: seizures, syncope or narcolepsy-cataplexy. All are clinical syndromes with more than one cause. Seizures are addressed in Chapter 7. Syncope due to cardiovascular disease is beyond the scope of this book. Narcolepsy-cataplexy is discussed below. Collapse may also occur as a result of more chronic, progressive neuromuscular diseases, which are also discussed below.

Paroxysmal disorders encompass a group of sporadically occurring disorders that often have no structural lesions within the nervous system. Each paroxysmal syndrome tends to manifest distinctive clinical signs and the animal is typically alert and responsive (i.e. without neurological deficits) between episodes.

# **Clinical signs**

Signs of episodic motor weakness include: an intermittent paretic gait, often manifested as a stilted stride that becomes progressively shorter with accompanying ventroflexion of the neck; reluctance to walk or run; lying down; and collapse. Ataxia may be present, suggesting upper motor neuron (UMN) or sensory deficits. The animal may be alert or depressed and may pant excessively. Muscle strength improves greatly following rest. In between the episodes of weakness, the animal may be completely normal or may have clinical signs of muscle disease (Figure 17.1) or nerve disease (see Chapter 14).

# **Lesion localization**

A thorough history, physical and neurological examination are essential to localize the lesion (Figure 17.2). It may be possible only to isolate a system (Figure 17.3), or a neurological or neuromuscular lesion may be suspected in one of the following areas (Figure 17.4): brain; diffuse spinal cord/nerve root; peripheral nerve; neuromuscular junction; or muscle.

Generalized weakness Exercise intolerance Stiff, stilted gait Localized or generalized muscle atrophy or hypertrophy Pain on palpation (myalgia) Contractures with chronic disease Ventroflexion of the head and neck (especially in cats) Regurgitation if oesophagus is involved

17.1 Principal clinical signs of muscle disease

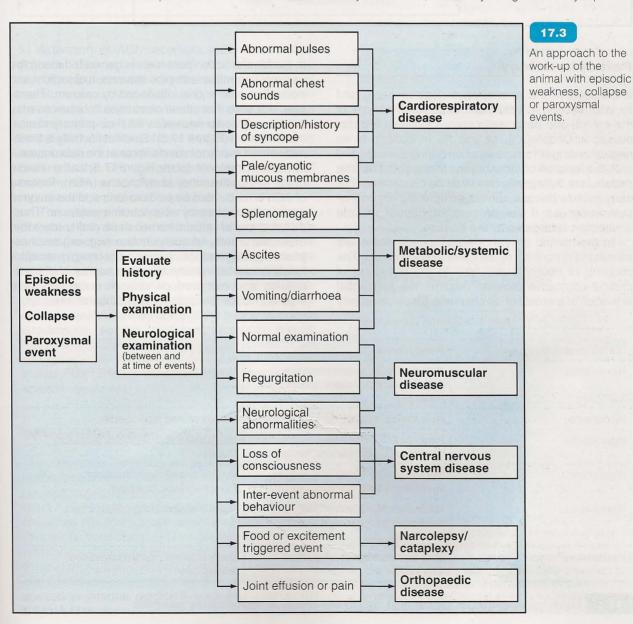
Question		Implications			
1.	What did the event look like?	It may be difficult to distinguish the event from seizure activity, and some may be seizure events, but it will be important to establish that these events are not due to a metabolic or cardiovascular crisis (see Figures 17.8 and 17.9).			
2.	Has this happened before?	Episodic or paroxysmal events that warrant investigation should be recurrent.			
3.	How often has this happened?	The answer will provide insight into the progressive nature of the disease and will serve as a marker for response to therapy.			
4.	Has it always had the same characteristics?	Paroxysmal events are usually stereotypical.			
5.	Is the animal 'normal' immediately after these events?	A seizure may be followed by a period of confusion, visual dysfunction, compulsion or even aggression. Stereotypical events, neuromuscular disorders and syncopal events usually have no such associations.			

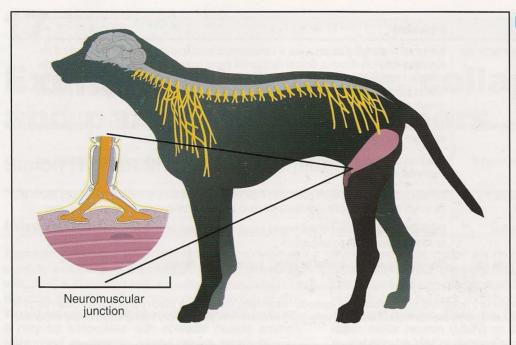
Important questions to ask about the episodic weakness, collapse or paroxysmal event. Often dogs or cats with these complaints are normal at the time of veterinary examination, thus history taking is extremely important. (continues)

17.2

Qu	estion	Implications		
6.	Is there any type of trigger factor that can be identified?	Excitement or eating that causes a loss of consciousness or collapse should prompt the thought of the narcolepsy/cataplexy disorders. Several documented events occur during sleep, such as the rapid eye movement sleep disorder. Exercise may be the trigger for the syndromes described in Cavaliers and Scotties as well as many neuromuscular diseases. Rarely, seizure events will be triggered by a specific noise or action.		
7.	Is the animal normal in between the events?	Any abnormalities described in between the episodes could indicate a structural CNS or systemic disease. Neuropathic or myopathic disease may have detectable signs on examination.		
8.	Are any other littermates known to be affected?	Breed-associated disease may be seen in related siblings; however, underlying infectious diseases and toxicities should not be ignored.		
9.	Is the animal stiff or floppy at the time of the event?	Stiffness at the time of the event would often imply either a seizure event or a myopathy. A floppy animal at the time of the event could be a myopathy but could also imply a cardiovascular or metabolic disease.		
10.	Are the gums pale at the time of the event?	Mucous membrane pallor could well indicate a cardiovascular disease; however, metabolic diseases such as Addison's should also be considered.		
11.	What are the heart and pulse rates at the time of the event?	Obvious tachy- or brady-arrhythmias indicate a cardiovascular disease.		

(continued) Important questions to ask about the episodic weakness, collapse or paroxysmal event. Often dogs or cats with these complaints are normal at the time of veterinary examination, thus history taking is extremely important.





Lesion localization for neuromuscular causes of collapse. Possible sites include the peripheral nerves, the neuromuscular junction (inset) and the skeletal muscles.

# **Pathophysiology**

Knowledge of the normal physiology of nerve and muscle function is essential. The basic physiology of the central and peripheral nervous systems are discussed in Chapters 8, 14 and 15. In addition to an understanding of muscle function during exercise and rest, the function of other organs that support muscle metabolism during exercise must be considered. Primary muscle disease can cause episodic or continuous weakness if the process of normal muscle contraction is targeted by the disease.

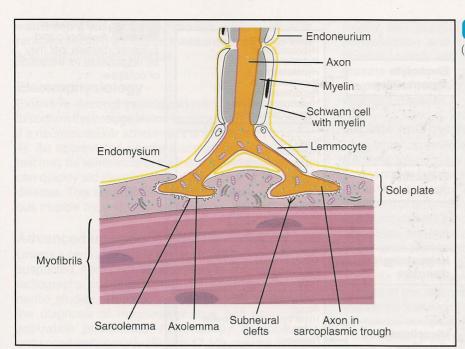
In the normal animal, skeletal muscle fibres are stimulated to contract by the lower motor neurons. The coupling of neuronal impulses to the activation of muscle contractile proteins requires the sequential activation of a variety of ion channels. Electrical activity

in the form of action potentials is generated along the nerve cell membranes by the movement of sodium and potassium ions and is influenced by calcium. Therefore, diseases that cause electrolyte imbalances may produce episodic weakness as their primary clinical manifestation (Figure 17.5). Electrical activity is transmitted from axons to muscle fibres at the neuromuscular junction (motor endplate; Figure 17.6) via the release of the neurotransmitter acetylcholine (ACh). Release of ACh is modulated by calcium ions and the enzyme itself is inactivated by acetylcholine esterase. Thus, disturbances of calcium homeostasis or disorders that affect the activity of acetylcholine (e.g. organophosphate toxicity) or post-synaptic cholinergic receptor function may adversely affect neuromuscular transmission and can produce episodic weakness (see Figure 17.5) or tetraparesis (see Chapter 14).

Electrolyte abnormality	Primary causes	Clinical signs  Muscle weakness; irregular cardiac rhythm	
Hyperkalaemia	Acute renal failure; hypoadrenocorticism; K <sup>+</sup> -sparing diuretics; metabolic acidosis; iatrogenic		
Hypokalaemia	Renal loss; intestinal loss; metabolic alkalosis	Muscle weakness; hypovolaemia	
Hypocalcaemia	Primary hypoparathyroidism; hyperphosphataemia; eclampsia; iatrogenic	Muscle weakness; tetany; mental depression; seizures	
Hypercalcaemia	Malignant tumours; primary hyperparathyroidism; hypervitaminosis D	Muscle weakness; mental depression; Polydipsia/polyuria; constipation	
Hyponatraemia	Intestinal loss; hypoadrenocorticism; inappropriate antidiuretic hormone (ADH) secretion; iatrogenic	Muscle weakness; lethargy; seizures; coma	
Hypernatraemia	Water deprivation; excess salt gain; pure water loss	Muscle weakness; muscle rigidity; tremors; seizures/coma	

17.5

Electrolyte abnormalities that can lead, directly or indirectly, to neuromuscular weakness.



Neuromuscular junction of a motor endplate (Redrawn after de Lahunta, 1983)

Activation of ACh receptors initiates an action potential. The action potential conducts along the myofibre and spreads into the cell via a series of membranous tubules (T tubules), where it stimulates the release of calcium ions stored within the sarcoplasmic reticulum (SR). Calcium ions then stimulate contraction of the myofibrils and are subsequently responsible for relaxation as they are sequestered back into the SR: therefore, the concentration of calcium ions within the body is critical for normal muscle contraction and relaxation.

The energy needed for muscle contraction is derived chiefly from the metabolism of carbohydrate and fat. During anaerobic exercise, the primary source of energy is muscle glycogen. Muscle glycogen can be rapidly depleted during exercise, and blood glucose then becomes the primary energy source. In hypoglycaemic conditions with a lack of this energy source, episodic weakness may occur. If the supply of oxygen is adequate, aerobic (oxidative) processes prevail. Lipid fuels in the form of fatty acids predominate and glucose is conserved. Disorders of oxidative metabolism of lipids or carbohydrate also result in episodic weakness.

# **Differential diagnosis**

The differential diagnosis will depend on the precise lesion localization. The differentials for each of the neuromuscular lesion localizations are listed in Figure 17.7. In young animals, primary considerations should be inherited, breed-associated (see Appendix 1) and infectious diseases. The differentials for seizure activity are discussed in Chapter 7. The differentials for metabolic and systemic diseases (Figure 17.8) and cardiorespiratory diseases (Figure 17.9) are discussed in internal medicine texts and appropriate BSAVA Manuals.

#### Myopathies

#### Non-inflammatory

Acquired:

Toxic; metabolic (endocrine)

Inherited:

Central core myopathy; muscular dystrophy; myotonia; metabolic myopathies a; Labrador Retriever myopathy

# Inflammatory

Infectious:

Viral; bacterial; rickettsial; protozoal

Immune-mediated:

Dermatomyositis; polymyositis

Paraneoplastic

Nutritional

#### Idiopathic

Exercise-induced collapse in Labrador Retrievers

Fibrotic myopathy
Exertional rhabdomyolysis

#### Neuromuscular transmission disease

Myasthenia gravis

Botulism to

Tick paralysis b

Snake bite b

Toxicity

#### Neuropathies °

Degenerative

Metabolic

Infectious Paraneoplastic

Idiopathic

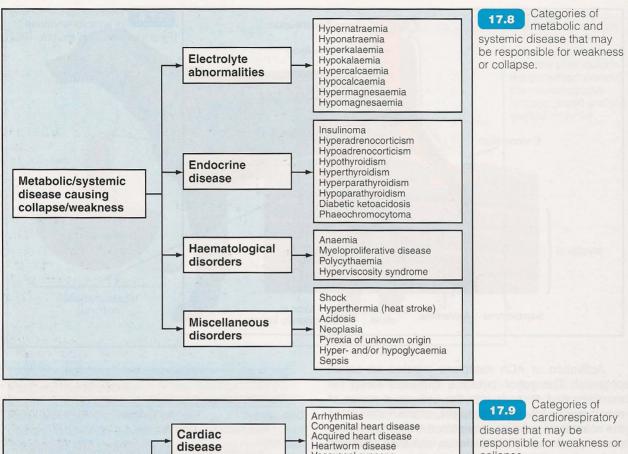
Traumatic

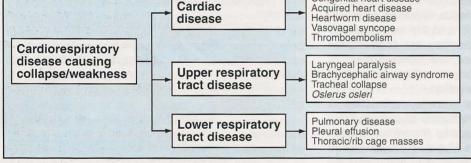
Toxic

Vascular

Categories of differential diagnoses that should be considered for neuromuscular diseases.

<sup>a</sup> Although most metabolic myopathies are not confirmed as inherited, it is likely that many could be classified as 'inborn' errors that are degenerative rather than inflammatory. b See Chapter 14 for a full description of these diseases. <sup>c</sup> See Figure 17.12 and Chapter 14.





collapse.

# **Neurodiagnostic investigation**

The diagnostic plan is dependent on the localization of signs, as well as their suspected underlying mechanism. As many of these problems are episodic, their frequency must be taken into account and it should be recognized that many of the tests will need to be performed at the time of the episode. The following tests should be considered for all cases with weakness or collapse, particularly if a neuromuscular disorder is suspected. Important questions to ask the owners about these events are detailed in Figure 17.2.

#### Video footage

If the episodes are so infrequent that they are not observed by the clinician, the owners should attempt to capture the event on videotape. Observation of the event is critical to the diagnosis. Without observation, the nature of the event must be surmised by listening to the 'eye-witness' description offered by the owner.

#### Minimum database

Comprehensive haematology, serum biochemistry including creatine kinase, lactate, electrolytes, urine analysis, a faecal examination and a resting electrocardiogram (ECG), as well as thoracic and abdominal radiographs, should be considered the minimum essential database. A thyroid panel and an adrenocorticotropic hormone (ACTH) stimulation test should also be considered, as neuromuscular disease may be the first and only manifestation of endocrine disorders. Resting blood pressure assessments should also be performed if there is any concern about a cardiorespiratory disease.

#### Serology

Investigations of infectious diseases may require extensive serological tests and their interpretation may be difficult but, depending on the potential for exposure, serology should be performed on all possible infectious candidates. Serology for autoimmune conditions such as rheumatoid arthritis, systemic lupus and myasthenia gravis may be

warranted if suspected. Antibodies against the ACh receptor (AChR) should be measured in all dogs with acquired megaoesophagus.

# Electrophysiology

Extensive electrophysiological testing may be required to confirm the precise lesion localization of the disease if a neuromuscular abnormality is suspected (Chapter 4). An abbreviated needle electromyography (EMG) test may be worthwhile in the initial investigations, as it can quickly aid identification of an axonal or muscular disease. This is particularly helpful in cases with obvious muscle hypertrophy or atrophy.

# Advanced imaging

Unless a central nervous system (CNS) abnormality is suspected, it may not be necessary to consider spinal radiographs, computed tomography or magnetic resonance studies. Thoracic radiographs can assist with the diagnosis of megaoesophagus and associated aspiration pneumonia. Fluoroscopy or contrastenhanced radiography (Figure 17.10) may be helpful to evaluate the function of the oesophagus if enlargement is not obvious on plain survey radiographs and cardiac ultrasonography may be required if a cardiorespiratory condition is suspected.

# Cerebrospinal fluid (CSF) analysis

A CSF tap may help to rule out CNS diseases as well as diffuse inflammatory conditions of the nerve roots, but rarely is it a specific test and rarely will it be helpful in cases of neuromuscular collapse (see Chapter 3). Evaluation for infectious diseases can be achieved with serological techniques or with polymerase chain reaction analysis of the CSF.

#### Muscle and nerve biopsy

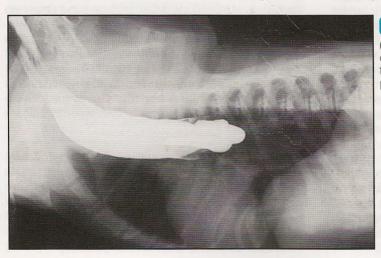
If a neuromuscular disease is suspected, a muscle or nerve biopsy can provide a specific diagnosis of the underlying cause (see Chapter 6). Since a peripheral nerve can react in only a limited number of ways to a variety of insults, the biopsy in most instances just confirms the presence of axonal degeneration, inflammation or demyelination. However, the nerve biopsy can provide information on regeneration, remyelination and degree of fibre depletion and fibrosis, which are important for prognosis. The muscle biopsy is of utmost importance in the diagnosis of most muscle diseases, particularly the inherited diseases.

# Lactate and pyruvate analysis

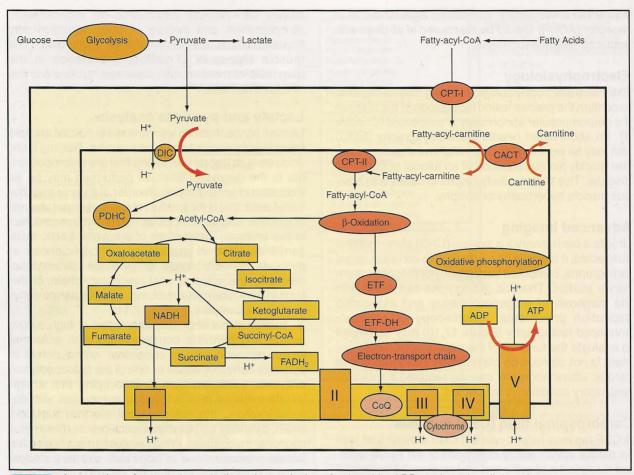
Lactate concentrations will increase in normal animals following strenuous anaerobic exercise. Resting lactic acidaemia or lactate elevations that are disproportionate to the degree of exercise performed may be an indication of an underlying disorder of muscle metabolism. Lactic acid is the product of anaerobic metabolism of glucose, and lactic acidosis can result from a defect in the anabolic metabolism of pyruvate. Lactic acidaemia develops in association with deficiencies in pyruvate dehydrogenase or pyruvate carboxylase, defects in the mitochondrial respiratory chain, or defects in the Krebs cycle involving  $\alpha$ -ketoglutarate dehydrogenase complex (Figure 17.11).

In human patients, documentation of high serum lactate and pyruvate concentrations with a normal lactate:pyruvate ratio is consistent with a defect in pyruvate dehydrogenase or one of the gluconeogenic enzymes. Lactic acidosis in association with a high lactate:pyruvate ratio is found in association with defects involving the mitochondrial electron transport chain, pyruvate carboxylase deficiency or other mitochondrial myopathies. When evaluating post-exercise lactate concentrations in dogs with exercise intolerance, it is essential to compare values obtained from the patient with those from appropriate control dogs. Lactate concentrations after exercise will vary depending on the duration and intensity of exercise performed (Platt, 2002).

Blood for lactate measurements should be collected into sodium fluoride/potassium oxalate tubes, the plasma separated and stored at  $-20\,^{\circ}\text{C}$  until analysed. Paired blood samples for pyruvate analysis should be mixed 1:1 with 10% perchloric acid, centrifuged and the supernatant removed and frozen at  $-20\,^{\circ}\text{C}$ ; samples should be submitted to laboratories on dry ice. Samples for both lactate and pyruvate analysis should be evaluated within 30 days.



A lateral radiograph demonstrating an abnormally large oesophagus (megaoesophagus) with the aid of barium contrast medium. When performing such studies, the risks of aspiration pneumonia in these patients should be considered.



An overview of selected metabolic pathways in the mitochondria. ADP = adenosine diphosphate;

ATP = adenosine triphosphate; CACT = carnitine-acyl-carnitine translocase; CoA = coenzyme A;

CoQ = coenzyme Q; CPT = carnitine palmitoyltransferase; DIC = dicarboxylate carrier; ETF = electron transfer flavoprotein;

ETF-DH = electron transfer dehydrogenase; FAD = flavin adenine dinucleotide; FADH<sub>2</sub> = reduced FAD; NADH = reduced nicotinamide adenine dinucleotide; PDHC = pyruvate dehydrogenase complex; TCA = tricarboxylic acid.

# **Peripheral neuropathies**

Figure 17.12 lists the acute and chronic peripheral neuropathies that should be considered for cases of episodic weakness or collapse and Chapter 14 gives a complete review of these disorders. In general, these diseases cause continuous rather than intermittent signs but exercise intolerance is often a feature.

# **Disorders of neuromuscular transmission**

Specific diseases affect neuromuscular transmission (see Figure 17.7), resulting in clinical signs that may be very similar to those of peripheral neuropathies or myopathies. Apart from the majority of cases with immune-mediated myasthenia gravis, these diseases often cause an acute onset of ascending weakness, progressing from the pelvic limbs to the thoracic limbs. Myasthenia gravis is discussed below. Chapter 14 gives a complete review of other disorders, including botulism, tick paralysis and snake bite paralysis.

Mechanism of disease	Motor neuron diseases Breed-specific neuropathies or laryngeal paralysis polyneuropathy complex		
Degenerative			
Metabolic	Diabetes mellitus Hypothyroidism Insulinoma or hypoglycaemia Hyperlipidaemia or hyperproteinaemia		
Neoplasia	Lymphoma Paraneoplastic		
Infectious	Polyradiculoneuritis – Toxoplasma, Neospora		
Idiopathic	Idiopathic polyradiculoneuritis (Coonhound paralysis) Chronic inflammatory demyelinating polyneuropathy Distal denervating disease Ganglioradiculoneuritis		
Toxic	Vincristine Cisplatin Organophosphates and carbamates		
Vascular	Ischaemic neuromyopathy		

17.12 Peripheral neuropathies responsible for episodic weakness and collapse (see Chapter 14 for a complete description of these diseases).

# Myasthenia gravis: immune-mediated

Immune-mediated myasthenia gravis (MG) is a relatively common neuromuscular disease affecting dogs and occasionally cats (Shelton, 2002). Acquired MG has been observed in dogs older than 3 months, of all breeds but particularly in German Shepherd Dogs, Golden Retrievers and Labrador Retrievers. In one report, the relative risk of acquired MG in different breeds of dog was highest in Akitas (Shelton et al., 1997). Newfoundlands may also be predisposed to acquired MG. A bimodal age of onset (< 5 years and > 7 years) has also been reported in affected dogs, and spayed female dogs may have heightened risk. In one review of cats with acquired MG, Abyssinians and the closely related Somalis seemed to be overrepresented and gender was not a risk factor (Shelton et al., 2000a).

#### Clinical signs

Several forms of MG have been described in dogs (Dewey *et al.*, 1997) including:

- Focal MG, with regurgitation, megaoesophagus or dysphagia being the only clinical signs. The incidence ranges from 26% to 43% of all cases of MG
- Generalized MG, with severe exercise intolerance and megaoesophagus reported in up to 57% of dogs with MG
- An acute fulminating form of generalized MG with a rapid onset of paralysis and megaoesophagus.

Generalized weakness without megaoesophagus occurs in approximately 30% of cats, generalized weakness and megaoesophagus/dysphagia occurs in 20% of cats, generalized weakness associated with thymoma occurs in approximately 26% of cats, while focal forms of MG, including megaoesophagus and dysphagia, without signs of generalized weakness occur in approximately 15% of cats. Affected dogs and cats may develop a stiff choppy gait, in which the stride shortens until they crouch in sternal recumbency and rest their head on their forepaws. After rest, they walk normally for a short period before repeating the cycle. Many animals have facial weakness; repeated stimulation of the palpebral reflex causes it to diminish. Many cats have facial weakness and are unable to close their eyelids (accompanied by lack of menace and absent palpebral reflex). Third eyelids may be protruded. Neurological examination may reveal normal sensation and intact tendon reflexes but diminished withdrawal reflexes, poor postural reactions and proprioceptive deficits. There is a greater incidence of mediastinal thymoma in cats with MG (25.7%) than in dogs (3.4%).

#### Pathophysiology

MG is characterized by failure of neuromuscular transmission due to reduction in the number of functional nicotinic ACh receptors on the postsynaptic membrane of the neuromuscular junction. This deficiency of functional receptors reduces the sensitivity of the postsynaptic membrane to the neurotransmitter,

acetylcholine (Shelton, 2002). Acquired canine MG is an immune-mediated disease caused by production of antibodies (predominantly IgG) directed against acetylcholine receptors (AChR-AB) of the neuromuscular junction. Based on experimental and human clinical studies, MG involves both B and T cells. Cell-mediated postsynaptic destruction of the neuromuscular junction and antibody-induced blockade of the function of the AChR molecules occur (Richman and Agius, 1994).

# Diagnosis

A presumptive diagnosis of MG may be made by the resolution of muscle weakness following the intravenous injection of edrophonium chloride (0.1 mg/kg i.v. in dogs, with a maximum 5 mg dose; 0.2–1.0 mg total dose in cats). This test may be useful in diagnosing focal myasthenia if a decreased or absent palpebral relex responds to edrophonium. A negative test does not rule out MG – either focal or generalized. Occasionally this test causes a cholinergic crisis of bradycardia, profuse salivation, miosis, dyspnoea, cyanosis and limb tremors, which can be reversed with atropine (0.05 mg/kg i.v.). Electrodiagnostics in the form of repetitive stimulation and single fibre electromyography can assist in the diagnosis. However, anaesthesia is necessary and this may be contraindicated in a critical patient.

The diagnosis of MG is confirmed in both dogs and cats by the demonstration of circulating AChR–AB in a serum sample. Reactive antibodies can usually be demonstrated in the sera of approximately 98% of dogs with acquired MG and in most affected cats. Antibodies reactive with muscle striations and other autoantibodies may coexist with a high titre of AChR-AB. In the absence of immunosuppressive therapy, there is a good correlation in dogs between the clinical course of MG and the AChR antibody titre. A thorough search should also be made for other autoimmune diseases that can occur concurrently with MG, including autoimmune haemolytic anaemia, thrombocytopenia and inflammatory bowel disease.

In dogs, acquired MG has also been reported in association with tumours, including cholangiocellular carcinoma, osteogenic sarcoma, anal sac adenocarcinoma and non-epitheliotropic cutaneous lymphoma; therefore, investigation for these tumours may be warranted. Acquired MG has also been reported in dogs with hypothyroidism, and in hyperthyroid cats receiving methimazole therapy. Chest radiographs should always be evaluated for a cranial mediastinal mass such as thymoma, and for aspiration pneumonia.

#### Treatment and prognosis

Treatment should begin with oral anticholinesterase drugs (pyridostigmine bromide 0.5–3 mg/kg q12h to q8h). The drug dosage should be started at the low end, to avoid cholinergic crisis, and can then be modified based on response. As noted above, cholinergic crisis manifests itself as a combination of bradycardia, profuse salivation, diarrhoea, dyspnoea, miosis, cyanosis and limb tremors. If oral treatment is not possible due to severe regurgitation, neostigmine can be given (0.04 mg/kg i.m. q6h).

If limb muscle strength has not returned to normal following anticholinesterase treatment or if intolerable side-effects of cholinergic excess are noted, and if there is no evidence of aspiration pneumonia, alternate-day low-dose corticosteroid therapy should be initiated (0.5 mg/kg orally). Immunosuppressive dosages of corticosteroids should be avoided early in the disease, as this can exacerbate weakness, but the steroid dose can be increased every 2 weeks up to an immunosuppressive daily dose (2 mg/kg) if necessary. Once a state of remission is achieved, the dose is reduced by 50% every 2–4 weeks whilst monitoring carefully for relapse. If there is no response to immunosuppressive doses of corticosteroids, azathioprine can be added to the regimen (2 mg/kg orally q24h).

Supportive care includes elevation of food and water or placement of a percutaneous enterogastrostomy (PEG) tube. Many dogs can be fed with food presented as small balls; the animal is then kept in a vertical position for 10 minutes to assist with the passage of food into the stomach. Water must also be offered, in reduced quantities, on a more frequent basis and from an elevated position.

Famotidine administered orally or via the PEG tube (0.5–1.0 mg/kg q12h) may reduce the nausea and gastrointestinal irritation from pyridostigmine. This may also be prevented by diluting liquid pyridostigmine 50:50 with water. Famotidine also helps to reduce oesophagitis due to acid reflux.

Concurrent hypothyroidism is treated with levothyroxine sodium (0.02 mg/kg orally q12h). Surgical removal of a cranial mediastinal mass is encouraged if the animal is clinically stable. Antibiotic therapy is essential if there is a suspicion of concurrent aspiration pneumonia.

The natural course of the disease in dogs, in the absence of an underlying neoplasia and without concurrent aspiration pneumonia, is clinical and immunological remission (Shelton and Lindstrom, 2001). Although surgical stress may exacerbate MG, heat cycles in females may make MG difficult to control and so intact females should be spayed. Vaccinations have also been shown to increase antibody titres and exacerbate weakness (Shelton, personal communication).

Periodic testing of AChR antibody titres should guide the course of therapy and treatment may be discontinued once the clinical signs have resolved (including radiographic resolution of a megaoesophagus) and once the antibody titre is well within the reference range. With the exception of a small number of cases, MG does not recur once remission is achieved. However, the prognosis in the early stages of this disease is guarded. In one report, up to 50% of dogs admitted to a referral hospital with myasthenia died or were euthanased within 2 weeks, often due to poor response to therapy and aspiration pneumonia (Dewey et al., 1997). The 1-year mortality rate for dogs with MG, previously estimated to be 40%, may be greatly improved through: early and accurate diagnosis; avoidance of immunosuppressive dosages of prednisolone early in the disease; and initiation of appropriate therapy.

# Congenital myasthenia gravis

Congenital myasthenic syndromes beginning at 6–8 weeks of age are rarely seen in dogs and cats. Congenital MG is thought to be an autosomal recessive trait in Jack Russell Terriers (Palmer and Goodyear, 1978), Smooth Fox Terriers (Miller *et al.*, 1983) and Springer Spaniels (Johnson *et al.*, 1975). A reversible form of congenital MG has been identified in young Miniature Dachshunds (Shelton, unpublished). Congenital MG has also been reported in several cats, including a Siamese (5 months of age) and Domestic Shorthair cats (4 and 7 months of age) (Joseph *et al.*, 1988). Presynaptic congenital MG has been reported in Gammel Dansk Hønsehund dogs (12–16 weeks old) with autosomal recessive inheritance (Flagstad *et al.*, 1989).

The diagnosis is made by clinical signs, an increase in muscle strength following the intravenous injection of edrophonium chloride, and documentation of a decremental response of the muscle action potential following repetitive nerve stimulation. Biochemical quantification of AChR concentration in an external intercostal muscle specimen may also be performed at a few research centres. As this is not an immune-mediated disease, testing for antibodies to AChR is not indicated. Animals may be maintained on oral anticholinesterase drugs for months to years. Drug resistance may develop over time.

# Organophosphate/carbamate toxicity

Organophosphate (OP) and carbamate compounds are widely employed for control of external parasites in dogs and cats and for control of insects in the home and garden. Both compounds inhibit acetylcholine esterase; the inhibition is irreversible in the case of organophosphates while carbamates cause reversible inhibition. Cats are relatively susceptible to acute toxicosis by the organophosphate compound chlorpyrifos.

# Clinical signs

The signs include those of a cholinergic crisis (excessive parasympathetic stimulation, skeletal muscle stimulation and central stimulation) varying with the compound involved and the individual susceptibility.

## Diagnosis

Diagnosis is by recognition of the signs and history of exposure, and can be confirmed by measurement of blood cholinesterase activity (see Chapter 3).

# Treatment and prognosis

Prompt treatment is often required with atropine and symptomatic support. Administration of atropine (0.2–0.4 mg/kg, slow i.v. administration) produces resolution of the muscarinic signs (e.g. salivation) and may need to be repeated at a lower dose if the signs recur. Atropine does not affect the nicotinic actions of acetylcholine at skeletal muscle. These can be improved in the case of organophosphate toxicity with prompt administration of pralidoxime chloride (2-PAM: dilute to 20 mg/ml and administer 20–50 mg/kg, by slow i.v., i.m. or s.c. routes; repeat q8h if needed). 2-PAM combines with organophosphates, producing

a non-toxic compound that can be excreted in the urine and reactivating acetylcholinesterase. It is only effective if given within 24 hours of exposure, before the enzyme/OP complex has aged to a non-reactive form; as it does not enter the CNS, 2-PAM does not affect CNS signs of toxicity. This drug is not effective against carbamate toxicity. Diphenhydramine has been used to treat refractory cases at a dose of 4 mg/kg orally q8h as it has both anti-nicotinic and muscarinic effects.

# **Drug toxicity**

Several drugs have been shown to reduce the safety margin of neuromuscular transmission, including aminoglycoside antibiotics, antiarrhythmic agents, phenothiazines and magnesium. These agents should be avoided in any patient with neurological weakness, particularly if associated with a disorder of neuromuscular transmission.

# **Myopathies**

# Non-inflammatory myopathies: acquired

#### **Nutritional myopathies**

Vitamin E (alpha tocopherol) deficiency has been reported to cause a myopathy in large animals but is rare in cats and dogs. Myalgia, weakness and sudden death may result, due the effects on the heart. Once the deficiency has been addressed, the myopathic signs may resolve.

# Endocrine myopathies: disorders of steroid metabolism

**Steroid myopathy:** Steroid myopathy may be overlooked in patients receiving steroid treatment for disorders that produce weakness, such as inflammatory myopathies or CNS diseases.

Clinical signs: Chronic corticosteroid therapy may result in dramatic muscle atrophy and weakness, particularly in dogs (Platt, 2002). Patients with steroid myopathy commonly have other clinical signs of glucocorticoid excess; skin and hair coat changes are typical (Figure 17.13). Patients rarely develop severe clinical weakness with < 4 weeks of steroid administration. Muscle atrophy, particularly of the masticatory muscles, may occur within 2 weeks of steroid therapy (Shelton, unpublished). It has been reported that steroid myopathy is more common after administration of the fluorinated corticosteroids such as triamcinolone, betamethasone and dexamethasone.

Pathophysiology: The major actions of glucocorticoids are to increase muscle protein catabolism and inhibit synthesis of myofibrillar proteins. Protein synthesis is inhibited primarily in type II muscle fibres and so net protein loss is greatest in these fibres. Inhibition of protein synthesis is dependent on the dose of steroids administered. Steroid myopathy is also associated with alterations in muscle carbohydrate metabolism, due in part to steroid-induced insulin resistance.



A 9-year-old Chinese Crested dog with a pendulous abdomen and thin skin due to hyperadrenocorticism. Alopecia was obviously difficult for the owner to detect in this breed of dog and so the condition progressed to loss of muscle mass and pelvic limb weakness.

Diagnosis: The diagnosis of steroid myopathy necessitates exclusion of other causes of generalized muscle disease, in addition to evidence of long-term steroid administration and muscle biopsy confirmation of disease. The typical pattern of type II fibre atrophy may be identified early in the course of steroid myopathy with muscle biopsy.

Treatment and prognosis: The treatment of choice for iatrogenic steroid myopathy is steroid dose reduction. Obviously, this can only be achieved if the condition that warranted treatment with corticosteroids is safely controlled. Conversion to a non-fluorinated steroid preparation and alternate-day treatment are recommended. Improvement may be seen but can take many weeks or longer. Because of the catabolic effect of corticosteroids, optimizing nutritional status is important. Protein supplementation in patients with a loss of muscle mass is recommended. Physical therapy may be useful in prevention and treatment of muscle weakness and wasting in patients receiving glucocorticoids. Androgens can partially antagonize the catabolic actions of alucocorticoids. The prognosis depends on how severe the muscle disease is at the time of diagnosis, as treatment may only prevent further deterioration rather than be responsible for improvement.

*Cushing's myopathy:* A myopathy has been described in dogs with spontaneous hyperadrenocorticism (Greene *et al.*, 1979).

Clinical signs: Most affected dogs are middle-aged; females are predisposed. Poodles and the smaller breeds are also over-represented. Affected dogs often, but not always, have characteristic signs of hyperadrenocorticism, in addition to generalized muscle atrophy and weakness. Of the cats that have been reported with Cushing's syndrome, the majority are middle-aged or older (average 10–11 years) and are usually of mixed breeding. Approximately 70% of the cats are female. No distinct myopathy has been reported in these cats but muscle wasting is a prominent finding.

Unilateral pelvic limb stiffness has been described as a frequent initial sign, with other limbs becoming gradually involved with time, but many dogs will have generalized muscle weakness and atrophy on presentation rather than generalized stiffness.

Pathophysiology: The myopathy found in Cushing's disease has been attributed to glucocorticoid excess, as described above for steroid myopathy. It has been suggested that elevated levels of ACTH may also be myopathic.

Diagnosis: The diagnosis necessitates exclusion of other causes of generalized muscle disease, in addition to biochemical confirmation of Cushing's disease and muscle biopsy evidence of type II myofibre atrophy. There may be mild serum creatine kinase (CK) elevation in some dogs. Electromyography investigation often reveals complex repetitive discharges, most consistently in the proximal appendicular groups.

Treatment and prognosis: Signs can resolve in some dogs over a period of months when they are treated for their primary disease, but deficits can persist. Improvement in motor function appears to be inversely related to the duration of disease prior to therapy. Dietary and physiotherapy treatments should also be instituted, as for steroid myopathy.

# Adrenal insufficiency:

Clinical signs: Muscle weakness, including reversible megaoesophagus and dysphagia, frequently occurs in association with hypoadrenocorticism (Addison's disease) in cats and dogs. Painful episodic muscle cramps affecting all four limbs have been reported in two Standard Poodles with Addison's disease (Saito et al., 2002). The dogs were neurologically normal between the episodes.

Pathophysiology: Adrenal insufficiency impairs muscle carbohydrate metabolism, water and electrolyte balance, muscle blood flow and adrenergic sensitivity, all contributing to the weakness associated with Addison's disease. Hyperkalaemia develops with depletion of muscle intracellular potassium, decreased membrane  $Na^+,K^+$ -ATPase activity, and diminished β-adrenergic stimulation of the  $Na^+,K^+$  pump.

*Diagnosis:* Exclusion of other causes of weakness is necessary as well as biochemical confirmation of Addison's disease.

Treatment and prognosis: The weakness and fatigue are usually rapidly corrected with glucocorticoid replacement. The prognosis is good with correction of the underlying endocrine disorder.

# Endocrine myopathies: disorders of thyroid metabolism

*Hypothyroid myopathy:* A myopathy occurs in dogs associated with hypothyroidism (Braund *et al.*, 1981).

Clinical signs: Neuromuscular signs including stiffness, weakness, reluctance to move and muscle wasting may be the first indication of an underlying endocrine disorder. Typical clinical signs of hypothyroidism, including lethargy, weight gain, seborrhoea and alopecia, may or may not be clinically evident.

Pathophysiology: In general, hypothyroidism affects carbohydrate, protein and lipid metabolism within muscle. Muscle glycogenolysis is impaired, protein synthesis and degradation is decreased, causing net protein catabolism, and muscle uptake of triglycerides is reduced.

Diagnosis: Serum CK concentrations may be normal or mildly elevated. Prominent histopathological alterations include variation in muscle fibre size with type II fibre atrophy and an increased population of type I fibres. Complex repetitive discharges can be detected in some dogs on electromyography.

Treatment and prognosis: The only effective treatment is to restore the patient to a euthyroid state. Once this is achieved, the prognosis for recovery is fair (Panciera, 1994). It is reasonable to institute physical therapy to limit disuse atrophy and joint contractures. There is no evidence that dietary manipulation improves muscle function in this disease.

Hyperthyroid myopathy in cats: Although specific pathological changes are lacking in muscles of hyperthyroid patients, there is a good correlation between severity of hyperthyroidism and clinical muscle weakness. In a study of 202 hyperthyroid cats, it was noted that 12% were reported as weak by the owners but only 1% exhibited a ventral neck flexion characteristic of muscle weakness in cats (Broussard et al., 1995). With more advanced disease, owners will report a decreased ability to jump and fatigue associated with physical exertion such that cats may lie down or rest when moving from one place to another, with breathlessness not uncommon. Hypokalaemia may be a complicating factor in cats with extreme weakness. known as thyrotoxic periodic paralysis in humans. In this condition, patients can have recurrent attacks of weakness, which can be precipitated by a carbohydrate challenge or rest after exercise. Muscle weakness should rapidly resolve following achievement of a euthyroid state.

# Non-inflammatory myopathies: inherited

# Muscular dystrophy

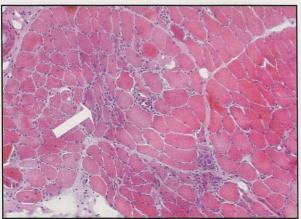
Muscular dystrophies are a heterogeneous group of inherited, degenerative, mostly non-inflammatory disorders characterized by progressive muscle weakness, muscle atrophy or hypertrophy, gait abnormalties and muscle contractures beginning in the first few months of life. While over 30 muscular dystrophies have been identified to date in humans, only a few have been characterized in dogs and cats. No specific therapies are currently available for any of the dystrophies and the general prognosis is poor. Affected animals should not be used in breeding programmes.

Muscular dystrophy with absence of dystrophin: Muscular dystrophy associated with dystrophin deficiency is the most common and best studied of the dystrophies in humans, and in dogs and cats (Valentine et al., 1992).

Clinical signs: Dystrophin deficiency has been documented in several breeds of dogs, including Golden Retriever, Rottweiler, German Short-haired Pointer, Irish Terrier, Groenendaeler Shepherd, Samoyed, Miniature Schnauzer, Brittany Spaniel, Rat Terrier, Pembroke Welsh Corgi and Labrador Retriever, and in Domestic Short-haired cats. An absence of dystrophin in dogs manifests primarily in males, causing generally diffuse muscle atrophy and hypertrophy of certain muscle groups (semimembranosus, semitendinosus and tongue muscles), and with generalized muscle hypertrophy in cats. Affected animals are exerciseintolerant. Dysphagia, regurgitation and dyspnoea may occur as a result of hypertrophy of the lingual, pharyngeal and oesophageal musculature and the diaphragm. Cardiomyopathy may result in heart failure.

Pathophysiology: Dystrophin links the myofibre cytoskeleton to the extracellular matrix and is crucial in stabilization of muscle fibre membranes during contraction. The dystrophin gene is located on the X-chromosome; thus, dystrophin deficiency is an X-linked recessive trait transmitted by a female carrier. Females with X-linked muscular dystrophy (produced from carrier female x dystrophic male breedings) may manifest milder clinical signs or be clinically normal, compared with the males, but have similar CK levels and comparable histological lesions.

Diagnosis: The serum CK concentration is usually markedly elevated (10,000–100,000 IU/I). Electromyography reveals complex repetitive discharges. A dystrophic phenotype is typically present on histopathology of muscle biopsy specimens (Figure 17.14). An absence of dystrophin on immunohistology of muscle specimens confirms the diagnosis.



A fresh-frozen muscle biopsy section from a young dog with muscular dystrophy shows necrotic fibres undergoing phagocytosis, clusters of basophilic regenerating fibres (arrowed), and endomysial fibrosis. Immunohistochemistry is needed to confirm absence of dystrophin and associated glycoproteins. H&E; original magnigfication X100.

Treatment and prognosis: There is no specific treatment. Prednisolone (0.5 mg/kg q24h) may improve the demeanour of affected dogs, especially if combined with physical therapy. The prognosis is poor.

# Muscular dystrophy with merosin (laminin $\alpha$ 2) deficiency:

Clinical signs: Muscular dystrophy associated with deficiency of laminin  $\alpha 2$  has been described in a young female Brittany—Springer spaniel mixed-breed dog presenting with gait abnormalities and generalized weakness from 8 weeks of age (Shelton et~al., 2001). Four unrelated cats (a young spayed Flame-point Siamese, two young female Domestic Short-hair, and a Maine Coon) were documented with a similar deficiency (O'Brien et~al., 2001; Poncelet et~al., 2003). Clinical signs in the cats varied from muscle weakness and atrophy to severe contractures with limb rigidity.

Pathophysiology: Laminin  $\alpha 2$  is the major component of the basal lamina that surrounds each muscle fibre and is one of the extracellular ligands that links dystrophin to the extracellular matrix, contributing to the stability of the muscle basement membrane. Deficiency of laminin  $\alpha 2$  is associated with autosomal recessive congenital muscular dystrophy in humans.

Diagnosis: Serum CK concentrations are moderately elevated (10 times normal) compared with the marked elevations found in dystrophin deficiency (may be 100 times normal). A dystrophic phenotype with endomysial fibrosis should be present on evaluation of muscle biopsy specimens. An absence of laminin  $\alpha 2$  on immunohistological analysis of muscle specimens confirms the diagnosis.

Treatment and prognosis: These are as for dystrophin absence

#### Recently identified canine muscular dystrophies:

Muscular dystrophy with an unusual truncated form of dystrophin has recently been identified in a family of Japanese Spitz dogs (Jones et al., 2004). Progressive clinical signs were first identified at 10-12 weeks of age and included excessive salivation and dysphagia, exercise intolerance and abnormal gait. Serum CK was moderately elevated in all reported dogs. A deficiency of the sarcoglycan complex, part of the dystrophin glycoprotein complex, has also recently been identified in three purebred dogs: an 11-month-old female Cocker Spaniel, a 7-month-old male Boston Terrier and a 5-month-old Chihuahua (Schatzberg et al., 2003). Sarcoglycan mutations are responsible for a subset of the human autosomal recessive muscular dystrophies known as the limb girdle muscular dystrophies. All three dogs presented for failure to thrive, lethargy and exercise intolerance as well as elevated CK concentrations.

#### Myotonia

Myotonia is a clinical sign defined as prolonged contraction or delayed relaxation of a muscle after voluntary movement or after mechanical or electrical stimulation.

Clinical signs: Myotonia is characterized by muscle stiffness without cramping, and muscle dimpling after palpation. Congenital myotonia has been described in the Chow Chow (suspected autosomal recessive) (Jones et al., 1977) and Miniature Schnauzer (autosomal recessive) (Vite et al., 1999) and in a series of related domestic kittens. Dental and craniofacial abnormalities were exhibited in affected Miniature Schnauzers. Single cases of congenital myotonia have been reported in a Great Dane, Staffordshire Terrier and Cocker Spaniel. In dogs, clinical signs of muscle stiffness (Figure 17.15) are evident at the time of first ambulation and are progressive: however, the signs can improve with exercise. Myotonia is accompanied by difficulty in rising, splaying of the limbs, a 'bunny-hopping' gait, muscle hypertrophy, regurgitation and stridor. Hypertrophied skeletal muscles are painless on palpation. Similar clinical signs have been documented in cats.



17.15 A 2-year-old Miniature Schnauzer exhibiting a stiff neck posture and marked prominence of the muscles over the proximal thoracic limb and neck. The dog was diagnosed with congenital myotonia. (Courtesy of Dr Charles Vite)

**Pathophysiology:** Myotonia is commonly due to diminished chloride conductance across the muscle membrane. This ionic abnormality results in increased sarcolemmal excitability. In some cases this is due to genetic defects in skeletal muscle ion channels (Vite *et al.*, 1998).

**Diagnosis:** Routine laboratory evaluations, including the serum CK concentration, are usually normal. Electrophysiological findings are characterized by waxing and waning myotonic discharges sounding like a 'revving' motorcycle. Muscle biopsy evaluation may reveal muscle hypertrophy or a type I fibre predominance without inflammation. For detection of the mutant allele in affected and carrier Miniature Schnauzers, a DNA-based test on whole blood has been developed and is available at the University of Pennsylvania (see Appendix 1).

**Treatment and prognosis:** Treatment is directed at decreasing the repetitive activity in the muscle by using antagonists to voltage-gated sodium channels. These drugs include extended-release procainamide (40–50 mg/kg orally q8–12h), quinidine, phenytoin and mexilitine (8.3 mg/kg orally q8h). The treatment has

been documented to improve but not normalize the condition; therefore, the prognosis depends on the severity of the clinical signs in the individual animal (Vite, 2002).

# Metabolic myopathies

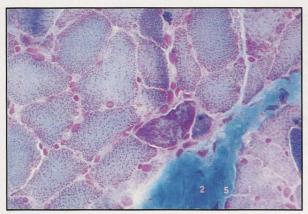
Metabolic myopathies are a group of muscle disorders caused by a biochemical defect of the skeletal muscle energy system, resulting in inefficient muscle performance. Although the metabolic myopathies reported in dogs have not all proved to be inherited, the suspicion is that they are at least 'inborn'. In recent years, a number of specific metabolic myopathies have been recognized in veterinary patients; however, they are generally still considered rare conditions.

# Mitochondrial myopathy

Very few confirmed cases of mitochondrial myopathy have been reported in dogs and cats, though mitochondrial dysfunction has been suspected in larger numbers. The combination of muscle and brain disease occurring in an animal should alert the clinician to the potential diagnosis of a mitochondrial disorder.

Clinical signs: A mitochondrial myopathy associated with deficiency of pyruvate dehydrogenase has been described in Clumber (Herrtage and Houlton, 1979) and Sussex Spaniels (Houlton and Herrtage, 1980; Abramson et al., 2004) from the UK and USA. The disease is characterized by poor exercise tolerance with development of severe metabolic acidosis, and lactic and pyruvic acidaemia. A mitochondrial myopathy with altered cytochrome-c oxidase activities and reduced mitochondrial mRNA has also been described in Old English Sheepdog littermates with exercise intolerance (Vijayasarathy et al., 1994). A Jack Russell Terrier presenting with progressive exercise intolerance and elevated blood lactate and pyruvate concentrations has been reported with the tentative diagnosis of mitochondrial myopathy (Olby et al., 1997).

Diagnosis: Evaluation of mitochondrial disorders requires analysis of resting and post-exercise blood lactate and pyruvate concentrations, blood gas analysis and specific assays of the enzymes involved in oxidative phosphorylation. Light and electron microscopic evaluation of mitochondria within muscle biopsy sections can be helpful in identifying abnormal mitochondrial accumulations and mitochondrial structure although such changes are non-specific. A classic finding on muscle biopsy is massive proliferation or enlargement of muscle mitochondria with subsarcolemmal accumulation, represented pathologically as 'ragged-red' fibres with the modified Gomori trichrome stain (Figure 17.16) and highlighted by oxidative enzyme localization (Platt, 2002). Biochemical analysis in the Sussex Spaniel from the UK and Clumber Spaniel from the USA demonstrated a defect in pyruvate oxidation (Shelton et al., 2000b). An MRI may show typical changes of metabolic brain disease (diffuse symmetrical hyperintensities often confined to the white matter).



Modified Gomori trichrome-stained muscle biopsy specimen from a dog with suspected mitochondrial myopathy. Subsarcolemmal and intermyofibrillar deposits of membranous material stains red with the trichrome stain, and represents accumulation of mitochondria. Myofibres with this staining pattern are called ragged-red fibres. Original magnification X400.

**Treatment and prognosis:** At present there is no cure for disorders of mitochondrial abnormalities and any treatment should be supportive, with a reduced daily level of activity. As for lipid storage myopathies detailed below, treatment with L-carnitine, coenzyme  $Q_{10}$  and riboflavin (Figure 17.17) may be attempted and can result in temporary stabilization of the disease (Abramson *et al.*, 2004).

Supplement	Dose regimen
Riboflavin	100 mg orally q24h
Coenzyme Q <sub>10</sub>	100 mg orally q24h
L-Carnitine	50 mg/kg orally q12h

Recommendations for treatment of mitochondrial and lipid myopathies.

#### Defects of glycogen metabolism

Glycogen storage diseases resulting from inborn errors of glycolysis or glycogen metabolism are rare myopathic disorders of dogs and cats (Figure 17.18). The enzyme defect results in inadequate glycogen utilization, frequently fasting hypoglycaemia, and accumulation of glycogen-like material within muscle and other tissue. Clinical signs include muscular weakness, exercise intolerance, collapse and occasionally seizures.

#### Lipid storage myopathy

*Clinical signs:* Dogs with abnormalities of lipid metabolism generally have chronic progressive signs of muscle weakness, atrophy and myalgia (Platt *et al.*, 1999).

**Pathophysiology:** Mitochondrial fatty acid oxidation is a vital source of energy production in all cells, especially skeletal and cardiac muscle. This complex pathway involves up to 20 individual steps, resulting in the formation of acetyl coenzyme A, which enters the TCA cycle and ultimately results in the production of ATP necessary for muscle contraction. The fundamental steps in lipid metabolism are: (1) transportation of fatty acids into skeletal muscle; (2) carnitine transport of fatty acids across the mitochondrial membrane; and (3) β-oxidation (see Figure 17.11). Other than secondary defects of carnitine metabolism, specific defects of β-oxidation have not yet been identified in dogs.

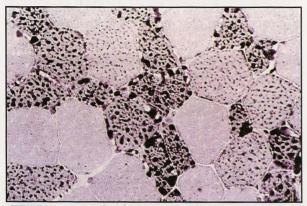
**Diagnosis:** The diagnosis of a lipid storage disorder is made by the demonstration of excessive droplets of neutral triglycerides in muscle biopsy specimens using Oil Red O staining (Figure 17.19). In addition to evaluation of a muscle biopsy specimen, determination of blood lactate and pyruvate concentrations, urinary organic acid and plasma amino acid quantifications, and plasma and muscle carnitine quantifications should be performed (Shelton *et al.*, 1998).

Type	Enzyme deficiency	Clinical signs	Diagnosis	Treatment
II (Pompe's disease)	Acid α-1,4-glucosidase	Reported in related Lapland dogs. Clinical signs develop in animals after 6 months of age, characterized by progressive muscle weakness, frequent vomiting and regurgitation, megaoesophagus, dysphonia, persistent panting and cardiac abnormalities. Death occurs before 2 years of age.	Low leucocyte activity of acid α-glucosidase	None
III (Cori's disease)	Amylo-1,6-glucosidase	Reported in German Shepherd Dogs and Akitas after 2 months of age, characterized by progressive muscle weakness, exercise intolerance ± hepatomegaly	Low leucocyte activity of amylo-1,6-glucosidase and PCR screening test	None
IV (Andersen disease)	α-1,4-p-glucan: α-1,4 glucan 6-glucosyl transferase	Reported in Norwegian Forest cats with fever, generalized muscle tremors, bunny-hopping gait, and weakness at 5 months of age which progressed to tetraplegia by 8 months	Branching enzyme activity < 10% of normal level in liver and muscle and PCR screening test	None

17.18 Glycogen storage diseases affecting the muscles. (continues)

Туре	Enzyme deficiency	Clinical signs	Diagnosis	Treatment
	Phosphofructokinase (PFK)	Reported in English Springer Spaniels less than 12 months of age; compensated haemolytic anaemia and sporadic episodes of intravascular haemolysis with haemoglobinuria; muscle cramping has been noted in affected field-trial dogs and in hunting dogs	Muscle and erythrocyte PFK activities are deficient and PCR screening test	None

17.18 (continued) Glycogen storage diseases affecting the muscles.



17.19 Fresh-frozen muscle section from a dog presented with exercise-related weakness and myalgia. The multiple large lipid droplets are indicative of a lipid storage myopathy. Oil red O; original magnification X400.

**Treatment and prognosis:** While no specific therapy is yet available for these disorders, treatment with L-carnitine, coenzyme  $Q_{10}$  and riboflavin (see Figure 17.17) may result in improvement in muscle strength and resolution of pain. The prognosis is fair to guarded.

# Hypokalaemic myopathy

Clinical signs: Clinical signs of muscle weakness in the cat become evident with any cause of potassium depletion, and include generalized weakness and ventroflexion of the neck (Figure 17.20). The most severely affected patients exhibit profound exercise intolerance accompanied by collapse. The weakness can ultimately result in paralysis and is progressive until the potassium deficit is corrected. The neurological examination is within normal limits.

Hyperthyroidism
Polymyositis
Hypokalaemic myopathy
Organophosphate toxicity
Thiamine deficiency
Hereditary myopathies (e.g. Devon Rex myopathy).

17.20 Causes of neck ventroflexion in the cat.

**Pathophysiology:** Hypokalaemic myopathy is seen in cats and very rarely in dogs, resulting from one of the following:

- Reduced potassium intake
- · Increased potassium entry into the cells
- Increased potassium loss from the body
- Familial disorder of electrolyte regulation (seen in Burmese kittens).

Hypokalaemia significantly affects muscle membrane activity and therefore muscle function (Fettman, 1989). The myocyte becomes increasingly refractory to depolarization in a hypokalaemic environment. Eventually the muscle cell membrane suddenly becomes permeable to sodium ions and membrane hypopolarization occurs, inducing an acute onset of severe weakness.

Diagnosis: The serum potassium level is often 1.5—3.5 mEq/l. Serum CK is often 500—10,000 IU/l. Chronic renal failure with urine loss of potassium should be ruled out with serum biochemistry and urine evaluations as well as imaging assessments of the structure and function of the kidney. The dietary potassium content should be investigated; diets should be at least 0.6% rich in potassium. Hyperthyroidism should also be ruled out. Electrophysiology may be normal or have areas of fibrillations and positive sharp waves (Chapter 4). Histological examination of muscle biopsies may be normal or show muscle fibre necrosis with little or no evidence of inflammation.

**Treatment and prognosis:** Potassium gluconate (2–4 mEq orally q12h) may be used in all animals. The dosage is adjusted until the serum potassium levels are normal. Adequate diet may be enough if insufficient potassium was the initiating cause but potassium supplementation may be needed for life in cats with renal disease. Severely affected cats may be treated with intravenous potassium chloride (0.2–0.4 mEq/kg/h diluted in intravenous fluids) with constant cardiac monitoring. The prognosis can be good if the potassium levels can be regulated or supplemented.

#### Miscellaneous myopathies

#### Exercise-induced collapse in Labrador Retrievers

Clinical signs: A syndrome of exercise intolerance and collapse has been observed in young adult (often 7 months to 2 years old) Labrador Retrievers of either sex, especially those used in field trials. Littermates and other related dogs have been affected with this condition but a confirmed genetic linkage has not been

documented. The dogs are normal at rest and with normal activity. They are usually very well muscled, athletic and excitable. Ataxia is usually noted after 5-15 minutes of strenuous activity, often followed by an episode of collapse, panting and distress. Patellar reflexes are lost during this time. The dogs usually return to normal after 10-20 minutes of rest, especially if passive cooling actions such as fans are used. A small percentage of dogs have died during the exercise period. Although dramatic elevations in body temperature after exercise (> 41.5°C) have been reported, a recent study has documented that normal Labradors demonstrate similar such elevations without collapse (Matwichuk et al., 1999). A similar syndrome has been seen in working Border Collies and Australian Shepherd Dogs (NJ Olby, personal communication, 2003).

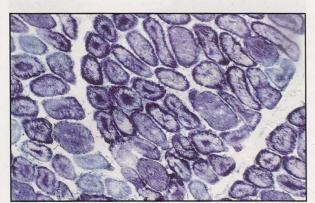
**Pathophysiology:** This is unknown but an inherited metabolic myopathy has been suspected.

**Diagnosis:** Apart from severe alkalosis on arterial blood gas analysis, all clinicopathological tests (including lactate:pyruvate ratios), electrophysiological and histopathological tests are normal.

**Treatment and prognosis:** The condition is not progressive and so a normal lifespan should be expected if the dogs are not heavily exercised. Exercise restriction is the only advice given at this time regarding treatment, especially when ambient temperatures are high. Hunting dogs may be less affected in cold weather.

#### Central core-like myopathy in Great Danes

Clinical signs begin at 6 months of age and consist of progressive muscle wasting, exercise intolerance, general body tremors and collapse exacerbated by excitement. Evaluation of muscle biopsy specimens shows well defined central cytoarchitectural changes that are highlighted by localization of oxidative enzyme activity (Figure 17.21). There is no known treatment at present and the disease is rapidly progressive and fatal (Targett et al., 1994).



Fresh-frozen muscle biopsy section from a young Great Dane with progressive muscle wasting and exercise intolerance. There are well defined central areas within several myofibres. Although dissimilar to the human disease, this is compatible with the central core myopathy described in the Great Dane breed. Oxidative reaction with NADH dehydrogenase; original magnification X100.

#### Labrador Retriever myopathy

Clinical signs: An autosomal recessive inherited myopathy, affecting both yellow and black Labrador Retrievers from 8 weeks to 11 months of age, causes a stiff 'bunny-hopping' gait with an abnormal 'low' head and neck posture and exercise intolerance. Tendon reflexes are absent or reduced. The signs are exacerbated by cold ambient temperature, exercise or excitement but tend to stabilize at 1 year of age. Affected dogs often have reduced muscle mass and a poor conformation, and working strains of Labrador are over-represented.

Pathophysiology: This disorder has been referred to as a polyneuropathy, muscular dystrophy, myotonia and a hereditary myopathy. The precise aetiology is unknown and there has been much debate about whether it represents a myopathy or neuropathy, as it has characteristics of both. Investigation of chronic pathological changes in a group of Labrador Retrievers with a similar phenotype has shown that the muscle pathology becomes more obviously myopathic with time (Blot, 2003). The term centronuclear myopathy has been proposed for this disease, as the majority of muscle fibres display centrally placed nuclei, with disorganized sarcoplasmic architecture in the long term. At present the gene responsible for the disease as well as its product are under investigation but the disease has been localized on canine chromosome 2 (CFA02) (Tiret et al., 2003). It is possible that more than one disease has been categorized as Labrador Retriever myopathy in the past, explaining the controversy as to the underlying aetiology.

Diagnosis: Serum CK is normal or mildly elevated in these dogs. Electromyography reveals fibrillation potentials, positive sharp waves and complex repetitive discharges. Nerve conduction studies are normal. Pathological changes within muscle biopsy specimens are variable and can include both neuropathic and myopathic abnormalities (McKerrell and Braund, 1986). There is usually dramatic variation in myofibre size, with small and large group atrophy. A few fibres display centrally placed nuclei and this percentage increases in the long term. A type II fibre deficiency has been described, as has endomysial fibrosis and occasional necrosis and regeneration.

**Treatment and prognosis:** Supportive therapy and avoidance of the cold are advised until the condition stabilizes. The disease itself is not lethal and so the prognosis is fair but dogs always have reduced exercise tolerance and will not be able to perform as working dogs.

## Fibrotic myopathy

This acquired, non-painful disorder associated with a fibrous band within a muscle has been reported sporadically in dogs – most commonly in German Shepherd Dogs, usually male, with an age range from 8 months to 9 years (Lewis *et al.*, 1997). Similar disorders have been reported in the Dobermann Pinscher, Rottweiler, St Bernard, Boxer and Old English Sheepdog.

Clinical signs: This may be a unilateral or bilateral disease. While onset in some dogs is acute, the gait deficit appears to be insidious in most dogs and is best seen when dogs are 'trotting'. In dogs with gracilis and/ or semitendinosus muscle involvement, the hindlimb gait is characterized by a shortened stride with a rapid medial rotation of the paw, external rotation of the hock, and internal rotation of the stifle during the mid-to-late swing phase of the stride, resulting in the paw being slapped to the ground prematurely. The gait anomaly results from restricted abduction of the coxofemoral joint and reduced extension of the stifle and hock.

Pathophysiology: Fibrotic myopathy has been called gracilis or semitendinosis myopathy, although any of the hamstring muscles can be affected, and a similar disease has been described affecting the infraspinatous muscle. A fibrous band can be palpated within the affected muscle belly and can extend the length of the muscle. Active dogs seem to be susceptible to this disorder and recent studies in dogs suggest that fibrotic myopathy may be related to muscle injury from excessive activity, including jumping and sprinting. It is proposed that muscle strain causes inflammation, oedema and localized haemorrhage, which leads to fibrosis (Steiss, 2002). Increased angulation (flexion) at the stifle in normal German Shepherd Dogs may predispose these dogs to increased hamstring stress during physical activity, explaining their over-representation.

**Diagnosis:** The gait is characteristic of the disease and neurological examination is usually normal. Tight fibrous cords are palpable in affected muscles. Serum CK levels may be normal or moderately elevated in some animals. Absence of myoelectrical activity in the band during EMG evaluation is consistent with total replacement of muscle fibres by dense connective tissue.

Treatment and prognosis: Prognosis is guarded to poor, since the condition in dogs tends to recur within several months following surgical resection of the fibrous band, or transection, partial excision or complete resection of the affected muscle. Non-surgical treatment (e.g. corticosteroids, non-steroidal anti-inflammatory drugs, acupuncture) is usually ineffective. Non-surgical rehabilitation, including therapeutic ultrasound and cross-fibre friction massage, resulted in mild improvement in several dogs (slight increase in range of motion of the stifle and less crossing-over of pelvic limbs). However, this disorder does not appear to be painful and simply causes a gait deficit: dogs can live with the disease without problem.

#### Exertional rhabdomyolysis (ER)

With the exception of racing Greyhounds and sled dogs, ER is rare.

Clinical signs: Clinical signs may occur during or within 24–48 hours of a race or trial and are characterized by extreme distress, hyperpnoea and generalized muscle pain, especially over the back and hindquarters, which may appear swollen and firm (Piercy et al., 2001). Limbs may be rigidly tonic and affected dogs may have a 'hunchback' appearance and refuse to

walk. Myoglobinuria and death within 48 hours are common in severe, acute cases.

**Pathophysiology:** In racing Greyhounds, severe lactic acidosis leading to muscle cell swelling, local ischaemia, muscle cell necrosis and myoglobinuria with nephropathy has been proposed as a likely sequence of events in the pathogenesis of ER (Bjotvedt *et al.*, 1983). Rhabdomyolysis may also occur sporadically in dogs as a complication of prolonged convulsive seizures (and extreme muscle exertion), babesiosis and malignant hyperthermia.

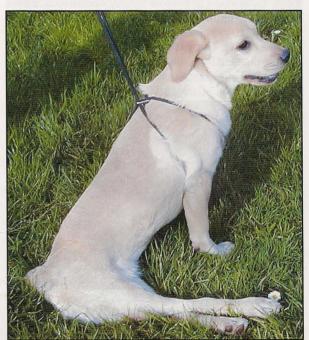
*Diagnosis:* Clinical signs associated with an acute episode of exertion should prompt suspicion. Serum CK may be markedly elevated. Urinalysis should be performed to rule out subsequent myoglobinuria. Electromyography investigation will be normal in acute muscle disease. Muscle biopsy will confirm rhabdomyolysis but, as time is of the essence for the treatment of this disease, it is rarely advised.

**Treatment and prognosis:** Treatment is mainly supportive with intensive fluid therapy being necessary to maintain normal renal function. Frequent blood gas analyses, biochemistry and urine analyses are advised, to monitor systemic acid—base status as well as kidney function. The prognosis is guarded.

# Inflammatory myopathies: infectious

#### Clinical signs

Signs seen in these patients are not specific but represent diffuse muscle disease; they include marked weight loss, weakness, exercise intolerance, generalized muscle atrophy, muscle pain (myalgia) and, in the late stages of disease, contractures and recumbency (Figure 17.22).



17.22 A 7-month-old Labrador Retriever exhibiting profound hyperextension of the pelvic limbs due to a *Toxoplasma* infection of the muscles and nerve roots of the lumbar plexus. Such contractures are often permanent.

# Pathophysiology

Inflammatory myopathies have been associated with protozoal, viral, rickettsial and, rarely, bacterial infections (Figure 17.23). Infections causing myopathies in dogs and cats are usually multisystemic. Protozoal and viral infections often become clinical in young animals in situations of immune compromise. Older animals may have concurrent infections or neoplastic diseases affecting local immunocompetence.

## Diagnosis

Diagnosis of an inflammatory myopathy necessitates muscle biopsy. Elevations of serum CK and abnormal needle EMG can be non-specific findings. Definitive aetiological diagnosis may be difficult as it relies upon the identification of organisms within the tissues, specifically with molecular or immunohistochemical methods;

however, *Toxoplasma* and *Neospora* spp. are often seen within the muscle. The interpretation of serological titres is particularly difficult in the acute stages of disease, because a single positive result only implies exposure to the disease, rather than clinical infection.

# Treatment and prognosis

The prognosis for most infectious inflammatory myopathies is guarded, but partial function may remain if treatment is initiated early in the course of the disease. If treatment is not initiated until the disease has reached a state of recumbency, it is unlikely that the patient will walk again. Intense physiotherapy may be needed in addition to specific antibiotics, especially in young patients that are continuing to grow in the face of severe muscle contractures caused by the infections.

Type of infection	Specific agent(s)	Clinical signs	Diagnostic tests <sup>a</sup>	Treatment	
Bacterial	Leptospira australis and L. icterohemorrhagiae	Fever, renal and hepatic disease in association with myopathy	Serology Urine culture	Management of renal failure Penicillin (25–40, 000 IU/kg i.v. q12–24h for 14 days) Doxycycline (5–10 mg/kg orally q12h for further 14 days)	
BURONITA URBER JERR URBER JERR URBER JERR	Clostridium	Severe focal or multifocal muscle pain. Infection associated with a previous muscle injury, surgery or injection	Gram stain Tissue/ blood culture	Surgical debridement Metronidazole (10 mg/kg orally q12h [dogs] / 62.5 mg orally q12h [cats] for 7 days) Clavulanated amoxicillin (22 mg/kg orally q12h for 7 days)	
Rickettsial	Ehrlichia canis	Diffuse muscle atrophy during acute phase of systemic disease	Serology	Doxycycline (5–10 mg/kg orally q12h for 14 days)	
Viral	Feline immunodeficiency virus	Can be asymptomatic but with periodic elevations of CK	Serology and Western blot	Zidovudine (AZT) Protease inhibitors	
Protozoal	Toxoplasma gondii Neospora caninum	Often accompanied by diffuse nerve root disease (polyradiculoneuritis) causing severe muscle atrophy and rigid pelvic limb hyperextension	Serology	Trimethoprim–sulphadiazine (15 mg/kg orally q12h for 4 weeks) Clindamycin (10 mg/kg orally q8h for 4 weeks) Pyrimethamine (1 mg/kg orally q24h for 2 weeks in dog)	
	Leishmania infantum	Bilateral masticatory muscle pain and atrophy without loss of jaw function; variable elevations of CK	Identification of amastigotes in Giemsa-stained lymph node or bone marrow aspirates	Antimonials Allopurinol (7–15 mg/kg orally q12h for 26 weeks)	
	Hepatozoon canis and H. americanum	Weight loss, fever, anaemia, neutrophilic leucocytosis	Identification of tissue stages in fixed muscle	Trimethoprim–sulphadiazine (15 mg/kg orally q12h for 4 weeks) Clindamycin (10 mg/kg orally q8h for 4 weeks) Pyrimethamine (0.25 mg/kg orally q24h for 2 weeks in dog) Decoquinate (10–20 mg/kg orally q12h indefinitely)	
	Trypanosoma cruzi (Chagas' disease)	Heart disease as well as generalized myopathy	Organism isolation Cytology of blood smear Serology	Benzimidazole (5 mg/kg orally q24h for 8 weeks)	

17.23

Infectious causes of polymyositis. <sup>a</sup> In addition to a minimum database, electrophysiology and a muscle biopsy.

# Inflammatory myopathies: immunemediated

# Idiopathic polymyositis

Clinical signs: Progressive exercise intolerance with acute exacerbation of weakness may occur but the disease may initially be episodic; marked weight loss is often reported by the owner (Figure 17.24). A stiff, uncomfortable gait in all limbs is often accompanied by an arched thoracolumbar spine (kyphosis) and a ventroflexed neck. Commonly, multiple skeletal muscles are affected, but it can manifest as a focal disease affecting pharyngeal, laryngeal, oesophageal or, infrequently, tongue muscle groups, causing dysphagia, dysphonia and stridor or regurgitation. Masticatory and extraocular myositis are covered in Chapters 11 and 9, respectively. Myalgia may be present but this is not a consistent finding (Evans et al., 2003). Pyrexia may be a feature of the disease or a consequence of aspiration pneumonia. Any age and breed of dog and cat may be affected.





Polymyositis in a 10-year-old Boxer with marked 17.24 generalized muscle atrophy. The dog initially presented with a complaint of dysphagia due to tongue dysfunction. The flaccid dysfunctional tongue seen here was also affected by the inflammatory process.

Pathophysiology: Idiopathic polymyositis is a generalized inflammatory myopathy affecting dogs and less commonly cats, not associated with any other systemic connective tissue disease or infectious cause. Tissue inflammation arises due to immune-mediated damage by lymphocytes.

Diagnosis: The diagnosis is based on identification of at least three of the following, including a confirmatory muscle biopsy (Podell, 2002):

- Appropriate clinical signs
- Elevation of serum CK concentration (at least 5-10 times the upper reference range) (CK can be low in end-stage disease)
- Compatible electrophysiological findings (see Chapter 4)
- Negative infectious disease titres
- Inflammatory muscle biopsy (critical for the diagnosis).

Treatment and prognosis: Early and aggressive institution of immunosuppressive therapy is essential for a good clinical outcome (Figure 17.25). The prognosis can be good unless there is concurrent megaoesophagus or pharyngeal dysfunction, or if therapy is not initiated until after there has been severe myofibre loss or fibrosis. Long-term treatment is usually required. The serum CK concentration should be monitored and immunosuppressive therapy continued until the CK returns to the reference range and clinical signs have resolved.

Antibiotic therapy if aspiration pneumonia is suspected or infectious cause cannot be ruled out. Depending on the condition of the patient, this should be instituted first and for up to 3 days prior to the use of corticosteroids

## Prednisolone:

Dogs 2 mg/kg Cats 3 mg/kg orally q12h for 14 days

Dogs 2 mg/kg Cats 3 mg/kg orally q24h for 14 days

Dogs 1 mg/kg Cats 2 mg/kg orally q24h for 14 days

Dogs 1 mg/kg Cats 2 mg/kg orally q48h for 14 days Taper to effect

Fentanyl patch for pain relief (25-75 µg/h) for first 3 days

If megaoesophagus, feed accordingly to avoid aspiration pneumonia

Azathioprine (if relapse or failure to respond) 2 mg/kg orally q24h until remission, then 0.5-2 mg/kg orally q48h

17.25 Treatment regimen for idiopathic polymyositis.

# **Dermatomyositis**

Dermatomyositis is a familial autosomal dominant inflammatory disease of striated muscles, skin and blood vessels of young Collies, Shetland Sheepdogs and, less commonly, Collie-crossbred dogs. An autoimmune pathogenesis is suspected. Dogs < 6 months old are most commonly affected, demonstrating a range of skin lesions on the face and ears and clinical signs similar to polymyositis. The temporalis and distal appendicular muscle groups are most commonly involved. Diagnosis requires histopathological evaluation



of skin and muscle. Treatment is for both the inflammatory myopathy and the skin lesions. The prognosis for animals with this disease also depends on the severity of the initial clinical signs.

# Inflammatory myopathies: paraneoplastic

A paraneoplastic polymyositis, sometimes associated with myasthenia gravis, has been described in dogs and cats diagnosed with thymoma. Myositis has also been diagnosed in dogs with malignant neoplasia such as myeloid leukaemia and carcinomas. Several Boxers with an initial diagnosis of polymyositis developed lymphoma within 1 year after the diagnosis of polymyositis (Evans *et al.*, 2003).

# Inflammatory myopathies: toxic or druginduced

Several drugs have been documented to produce an inflammatory myopathy either experimentally or in clinical cases. Penicillamine and cimetidine have been reported to produce polymyositis. There have been sporadic reports of a severe myopathy in dogs associated with ingestion of dog food contaminated with monensin, a coccidiostat and feed additive used for chickens and cattle (Wilson, 1980).

# **Paroxysmal events**

Paroxysmal events are characterized by the sudden and reversible onset of neurological dysfunction in an otherwise normal animal. The animals do not lose consciousness and rarely have a structural lesion identifiable within the CNS. The underlying cause of many of these events may be a functional abnormality related to neurotransmitter imbalances or receptor abnormalities and dysfunction. Several stereotypical events have been described in specific breeds and are discussed below. Confirmation of the specific syndrome is difficult or impossible in the clinical setting but depends heavily on the exclusion of structural CNS abnormalities such as neoplasia, inflammation and cerebrovascular disease. The questions that need to be answered are similar to those relating to seizure events and are listed in Figure 16.2.

#### **Breed-related disorders**

#### Scotty cramp

Clinical signs: Clinical episodes are most commonly seen in Scottish Terriers from 6 weeks to 18 months of age and may be elicited by stress, excitement or exercise. The thoracic limbs are initially affected, becoming abducted shortly after exercise begins; this is followed by arching of the lumbar spine and pelvic limb stiffness, which can progress to somersaults, falling, and tightly flexed pelvic limbs. Loss of consciousness is not a feature and the signs resolve within 10 minutes, but can recur multiple times over a 24-hour period. Similar conditions have been described in Dalmatians, a Cocker Spaniel, a Wirehaired Terrier and in Norwich Terriers.

**Pathophysiology:** This recessively inherited non-progressive disorder is thought to be associated with relative deficiencies of the inhibitory neurotransmitter 5-hydroxytryptamine (serotonin) (Meyers *et al.*, 1973).

**Diagnosis:** All laboratory tests are within normal limits. Signs can be induced with exercise 2 hours after using methylsergide (0.3 mg/kg orally), a serotonin antagonist.

Treatment and prognosis: Treatment consists of daily oral dosing of acepromazine maleate (0.1–0.75 mg/kg q12h) or diazepam (0.5 mg/kg q8h). Vitamin E (125 IU/kg/day) has also been advised for these dogs. Non-steroidal anti-inflammatories are contraindicated. Prognosis is fair, as the disease is non-progressive; appropriate lifestyle changes can result in a good quality of life.

# Hypertonicity (hyperexplexia) in Cavalier King Charles Spaniels

This condition, also known as 'episodic falling' in Cavalier King Charles Spaniels, has been described in the UK, USA and Australia and is suspected to have an inherited component.

Clinical signs: The syndrome is often seen in animals between 3 and 7 months of age. Variable periods of exercise induce a bounding pelvic limb gait in which the limbs may be abducted and appear stiff. This may progress to 'bunny-hopping', arching of the spine and collapse. As in Scotty cramp, the animals are normal between the events, there is no loss of consciousness and the events may be triggered by stress and excitement.

**Pathophysiology:** The pathogenesis is at present unknown but preliminary studies implicate an abnormality of CNS neurotransmission.

**Diagnosis:** Laboratory tests and electrodiagnostic examinations are normal. Therefore diagnosis is by exclusion and correlation of an appropriate history with clinical signs.

**Treatment and prognosis:** Treatment with the benzodiazepine drug clonazepam (0.5 mg/kg q8h) can result in almost complete remission of the signs (Garosi *et al.*, 2002) but tolerance to this drug does develop.

# Lafora's disease (myoclonic epilepsy) in Miniature Wirehaired Dachshunds

Familial myoclonic epilepsy with similarities to Lafora's disease in humans has been reported in several Miniature Wirehaired Dachshunds (Fitzmaurice *et al.*, 2000).

Clinical signs: Presenting clinical signs include repetitive muscle contractions (twitching), seizures and jerks in response to visual, auditory or sensory stimuli. Age of onset has ranged from 6 to 13 years, with both males and females affected.

Pathophysiology: This is unknown.

**Diagnosis:** Neurological examinations and routine laboratory and CSF evaluations are within the normal range. The presence of intense periodic acid-Schiff positive, diastase-resistant inclusions (polyglycosan bodies) in fresh frozen muscle biopsy specimens may aid in establishing the diagnosis in cases with a consistent clinical phenotype.

**Treatment and prognosis:** Phenobarbital therapy at standard anticonvulsant doses may result in some clinical improvement of the seizure activity but has not been completely successful in the authors' experience. The prognosis depends on the frequency and severity of the events and how these affect the dog's quality of life. Similar pathology has been described in older Beagles and Bassett Hounds.

# Familial reflex myoclonus

Clinical signs: This disease has been reported in Labrador Retrievers from about 3 weeks of age (March et al., 1993). The disorder is characterized by paroxysmal muscle spasms and progressive muscle stiffness leading to recumbency, with opisthotonus seen in response to voluntary activity or external stimuli. The animals are normal at rest.

**Pathophysiology:** A defect in glycine or its receptor, the major inhibitory neurotransmitter in the spinal cord, has been suggested as the basis for this disorder.

**Diagnosis:** The diagnosis is made by exclusion in addition to correlation of history and clinical signs. The dogs have no evidence of a muscle disease on clinical or histopathological examination and have normal laboratory tests. Electromyographic changes are characteristic.

**Treatment and prognosis:** Therapeutic trials have been disappointing but diazepam (0.5–2.0 mg/kg orally q8h) and/or phenobarbitone (2.2–5.0 mg/kg orally q12h) may provide some relief from the spasms. The prognosis is poor.

# Sleep disorders

# Narcolepsy-cataplexy

Narcolepsy is a disorder of sleep/wake control characterized by a tendency to fall asleep during the day, disturbed night-time sleep patterns and cataplexy. Cataplexy refers to sudden loss of motor tone ranging in severity from a dropped jaw to complete collapse without loss of consciousness and it represents a disorder of rapid eye movement (REM) sleep. Narcolepsy has been reported in many canine breeds, including Dobermann Pinscher, Labrador Retriever, Miniature Poodle, Beagle and Dachshund. Autosomal recessive inheritance of the trait was established in Dobermann Pinschers and Labrador Retrievers and linked to a region of chromosome 12 that was termed the canarc-1 gene in both breeds. Subsequent work has shown that there are mutations in the hypocretin (orexin) receptor 2 gene (Hcrtr2) (Lin et al., 1999) in this region.

Clinical signs: The predominant signs in dogs and cats is cataplexy but excessive daytime sleepiness and fragmented sleep patterns have also been reported. Cataplexy is characterized by paroxysmal attacks of flaccid paralysis without loss of consciousness and may last up to 20 minutes, with a sudden return to normality. The event is not accompanied by faecal or urinary incontinence, salivation or rigidity of muscle groups. The episodes, which may occur multiple times a day, are frequently induced by excitement such as eating or playing and they can be reversed by verbal or tactile stimuli. Cataplexy has been recorded in puppies and adult dogs but usually begins in the first 6 months of life with the establishment of REM sleep.

Pathophysiology: The pathogenesis of this disorder remains uncertain; however, an imbalance between cholinergic and catecholaminergic neurotransmitter systems within the CNS appears to be involved. Recent studies point to hypocretins (orexins) as important sleep-modulating neurotransmitters (Lin et al., 1999). The hypocretins (orexins) are two novel hypothalamic neuropeptides (Hcrt-1 and Hcrt-2), derived from the same precursor gene, that are synthesized by hypothalamic neurons. Defects in hypocretin neurotransmission and hypocretin deficiency appear to play an important role in narcolepsy. Indeed there is a recent report of a narcoleptic Chihuahua with decreased CSF hypocretin concentrations (Tonakura et al., 2003). Autoimmunity is additionally considered by some researchers to play a role in the development of narcolepsy, in view of the rarity of hypocretin receptor mutations in humans and a genetic link to a human leucocyte antigen (HLA) locus.

*Diagnosis:* Diagnosis is based on typical clinical signs, though analysis of CSF hypocretin levels may become available in the future. Attacks can be induced in most affected animals by exercise or eating. Signs can be alleviated for up to 45 minutes using imipramine (0.5 mg/kg i.v.). Atropine sulphate (0.1 mg/kg i.v.) is also reported to be a useful diagnostic test, providing immediate temporary remission of signs for up to 3 hours.

**Treatment and prognosis:** The disease may not be progressive with respect to frequency or severity of the events but it can obviously affect the animal's quality of life. Long-term treatment with tricyclic antidepressants such as imipramine hydrochloride (0.51.5 mg/kg orally q8–12h) has been recommended. Methylphenidate hydrochloride has also been described as effective at a dose of 0.25 mg/kg q12–24h.

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# Tail, anal and bladder dysfunction

Joan R. Coates

### Introduction

Lesions that cause tail, anal and bladder dysfunction can involve the S1 to coccygeal (also known as caudal) spinal cord segments and nerve roots; together with the L7 nerve roots these structures form the cauda equina. The sacral spinal cord segments (S1–S3) innervate the detrusor muscle of the bladder (pelvic nerves) and the external anal and urethral sphincters (pudendal nerve). Neurons from the S1 spinal cord segment also contribute to the sciatic nerve. The coccygeal spinal cord segments provide motor and sensory innervation of the tail (via the coccygeal or caudal nerves). Because of the potential for causing incontinence, diseases affecting these structures can have extremely serious ramifications for both the patient and the owner.

# **Clinical signs**

Clinical signs of sacrococcygeal spinal cord dysfunction, also referred to as cauda equina syndrome, reflect sensory, motor and autonomic disturbances.

- Gait is affected if the sciatic nerve is involved; lameness, ataxia (loss of proprioception) and paresis (weakness) can occur. The femoral nerve is unaffected by lesions in this location, therefore pelvic limb paralysis (or paraplegia) should not ensue.
- The pelvic limbs may show decreased withdrawal reflexes and muscle tone (Figure 18.1).
- Radicular pain or nerve root signature characterized by flexion and limited weight bearing of the affected pelvic limb can occur.
- Signs of tail dysfunction include low carriage, loss of 'wag', reduced tone and reduced to absent sensation (Figure 18.2).
- With sacral nerve dysfunction, the perineal reflex is reduced or absent and anal sphincter tone is reduced on digital rectal palpation. This can result in faecal incontinence. Sensory disturbances are characterized by reduced or absent perineal sensation.
- Paraspinal hyperaesthesia may be elicited upon palpation of the lumbosacral region or upon tail manipulation (Figure 18.3).



Pelvic limb of a 5-year-old Labrador Retriever showing decreased withdrawal (flexor).



A 10-year-old mixed-breed dog showing signs of tail dysfunction and loss of 'wag'.



Palpation of the lumbosacral region in a 10-year-old female spayed, German Short-haired Pointer dog to elicit paraspinal hyperaesthesia.

 The bladder is usually easily expressed if the urethral tone is reduced. The detrusor reflex may be lost, and urine dribbling results from overflow of a full bladder. (Normal and abnormal micturition is addressed separately below.)

# **Lesion localization**

The first to third sacral, and the coccygeal spinal cord segments are responsible for innervation of the tail, anus and bladder. The sacral segments are invariably located over the body of the fifth lumbar vertebra and the five coccygeal segments are located over the sixth lumbar vertebra in dogs (Figure 18.4). In cats they are situated further caudally. The sacral nerves arising from these spinal segments pass over the seventh lumbar vertebra and the lumbosacral junction (as the cauda equina) before exiting through foramina in the sacrum and between the coccygeal vertebrae.

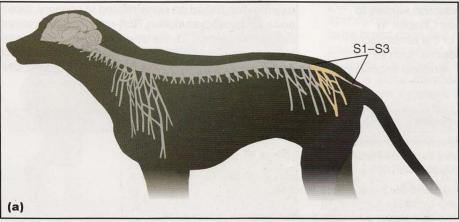
It is important to be aware that lesions of the vertebral canal between L7 and S1 can affect all or part of the sacral and caudal nerves, in addition to the seventh lumbar spinal nerve which exits through the L7 and S1 intervertebral foramen. Lesion localization for bladder dysfunction is addressed in the section on Normal and abnormal micturition.

# **Pathophysiology**

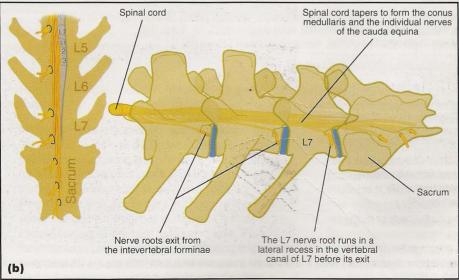
As for spinal cord diseases, lesions of the sacro-cocygeal region can be anomalous, compressive, concussive, inflammatory or vascular. However, this region is distinct from other areas of the vertebral column because it contains the peripheral nerve roots of the cauda equina, rather than the spinal cord. Peripheral nerves are more resistant to injury than neurons in the central nervous system (CNS) and have a robust regenerative response (see Chapter 16).

Although the nerve roots found in the canal are more sensitive than the nerves themselves, they can be manipulated carefully during surgery without detrimental effect, and traumatic luxations of the lumbosacral junction can occur without permanent nerve damage.

An additional consideration is that the lumbosacral area is prone to disease because the lumbosacral junction is a mobile part of the spine responsible for transmitting the propulsive force of the pelvic limbs to the rest of the spine, and also because of its developmental complexity. (For information on the pathophysiology of urination see Normal and abnormal micturition below.)



(a) Lesion localization for disorders of the tail, anus and bladder; the sacral cord segments and associated nerves (S1–S3) are highlighted. (b) A dorsal (left) and lateral (right) schematic overview of the caudal lumbar and lumbosacral vertebrae and associated nerve tissue.



# **Neurodiagnostic investigation**

Signalment and history are important to assist with the differential diagnoses associated with tail, anus and bladder dysfunction. Urinary and/or faecal incontinence are established and characterized by determining the frequency and animal's awareness of voiding, along with an accurate description of urination and defecation. For example: does the animal strain to defecate and does the process appear painful to the animal? A history of trauma is important as tail, anal and bladder disorders are also associated with traumatic events such as animal bites and vehicular injury.

A recommended diagnostic approach to disorders of sacrococcygeal spinal cord diseases is as follows:

- Complete blood count (CBC), serum biochemistry profile and urinalysis to detect other metabolic illnesses
- Thoracic radiographs in animals >5 years of age and after trauma
- Abdominal radiographs and ultrasonography may detect sublumbar masses and abnormalities of the caudal abdomen
- Cerebrospinal fluid (CSF) collection preferably from the caudal lumbar region to identify inflammatory disease
- Electrodiagnostics, i.e. electromyography (EMG), to detect muscle abnormalities secondary to denervation and nerve conduction studies to evaluate specific nerves (see Chapter 4)
- Survey spinal radiographs of the lumbosacral spine to identify vertebral lesions such as discospondylitis, fractures, vertebral anomalies and vertebral neoplasia

- Epidurography outlines the cauda equina but can be difficult to interpret (see Chapter 5)
- Myelography is less useful to diagnose compressive spinal cord disease in the lumbosacral region because the subarachnoid space (and therefore the contrast media) may not descend far enough caudally to outline the cauda equina, particularly in large dogs
- Computed tomography (CT) and magnetic resonance imaging (MRI) are the most useful techniques to delineate bone and soft tissue structures associated with the cauda equina.

Additional diagnostic procedures include urine culture, culture of disc aspirates, CSF protein electrophoresis, serology and exploratory surgery.

# Disorders of the tail, anus and bladder

The causes of tail, anal and bladder dysfunction are summarized in Figure 18.5.

# Degenerative diseases

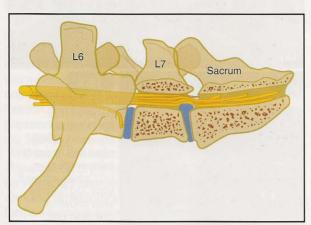
# Degenerative lumbosacral stenosis

Clinical signs: Neuroanatomical localization to the lumbosacral region is determined by the neurological examination based on signs related to sensory, motor and autonomic dysfunction. Non-specific observations include reluctance to rise and pelvic limb lameness. Neurological signs commonly include pain and motor dysfunction as a result of lower motor neuron (LMN) weakness (sciatic, pudendal, coccygeal nerve).

Mechanism of disease	Specific diseases
Degenerative	Degenerative lumbosacral stenosis [18] Intervertebral disc disease (Hansen types I and II) [14 and 15] Spondylosis deformans [13]
Anomalous	Vertebral and spinal cord anomalies [5, 13, 15 and 18] Vertebral – sacrocaudal dysgenesis [18] Primary vertebral anomaly with associated cord abnormalities – spina bifida [18]
Neoplastic	Extradural – chordoma [18], metastasis, vertebral tumours (sarcomas, plasma cell tumours), lymphoma [15] Intradural – extramedullary – meningiomas [15], nerve sheath tumours [16], lipoma [18] Intramedullary – ependymomas, gliomas, metastasis, round cell tumours [15]
Inflammatory	Discospondylitis/osteomyelitis/physitis [13 and 15] Tail abscessation [18] Granulomatous meningoencephalomyelitis [10] Infectious meningoencephalomyelitis [10 and 15] Steroid-responsive meningitis—arteritis [13]
Idiopathic	Diffuse idiopathic skeletal hyperostosis [15] Dysautonomia [18]
Traumatic	Lumbosacral fracture/luxation [18] Sacrocaudal luxation [18] Sacral fractures [18]
Vascular	Fibrocartilaginous embolism [14 and 15] Limber tail [18]

Causes of tail, anal and bladder dysfunction. Note the numbers in square brackets indicate the Chapter in which the disease is discussed in detail.

Pain is the most consistent clinical sign and reflective of compressive or inflammatory processes affecting pain sensitive structures (nerve root, meninges, periosteum and joints) (see Chapter 13). It is the opinion of the author that the pain primarily originates from nerve root (radicular pain) compression (particularly L7; Figure 18.6). The affected patient often stands with the pelvic limbs tucked under the caudal abdomen to flex the spine and lessen nerve root compression (Figure 18.7).



18.6 A sagittal section of the L7 vertebra, the intervertebral disc space and the sacrum demonstrating disc protrusion and nerve root compression.



18.7 A 6-year-old Rottweiler with degenerative lumbosacral stenosis. Note that the pelvic limb is tucked under the caudal abdomen in order to flex the spine and lessen nerve root compression.

Pain is manifested by hyperaesthesia and/or paraesthesia.

- Hyperaesthesia is elicited upon palpation of the lumbosacral joint or by hyperextension of the pelvic limbs causing the spinal region to have lordosis. This accentuates canal stenosis and nerve root compression, causing pain.
- Paraesthesia is caused by irritation of the nerve roots without an external stimulus. Clinical signs include biting at the tail, rump and feet. Pain of lumbosacral origin is also exacerbated with exercise as an asymmetrical lameness and is termed neurogenic intermittent claudication.

Motor dysfunction varies in severity. The patient may have mild to severe gait and postural reaction deficits. The gait is frequently short-strided or shuffled. Postural reaction deficits are often asymmetrical depending upon the degree of cauda equina involvement.

Reflex dysfunction of the limbs commonly involves those muscles innervated by the sciatic nerve (L6–S1 nerve roots but L7 and S1 provide the major contribution) particularly the flexor and extensor muscles of the hock. The patellar reflex may be hyperreflexic due to loss of antagonism from the flexor muscles (pseudohyperreflexia). The cranial tibial and gastrocnemius reflexes may be hyporeflexic. The flexor withdrawal reflexes are reduced in the stifle and hock joints. Less commonly the pudendal and coccygeal nerves may be involved. The pudendal nerve (S1, S2 and S3) innervates the perineal region including the external anal and urethral sphincters. The coccygeal nerves innervate the tail. Decreased tail tone is assessed upon palpation and inability to wag.

Other less common clinical signs include faecal and urinary incontinence. If micturition dysfunction is suspected it is important to closely evaluate sensory perception of the perineal region and the anal reflex. A digital rectal examination will assess rectal tone, the urethra and prostate.

Pathogenesis: Lumbosacral stenosis (LSS) (cauda equina syndrome, lumbosacral malarticulation and malformation, lumbosacral instability, lumbosacral spondylopathy) is common in middle- to old-aged, large breed dogs and represents a plethora of orthopaedic abnormalities associated with the lumbosacral anatomy (De Risio et al., 2000). Neurological abnormalities occur coincident with tissue (joint capsule, interarcuate ligament, disc, bone, fibrous adhesions) impingement on to the cauda equina, the nerve roots at the level of the foramina, or the vascular supply. The pathological process begins with Hansen type II disc degeneration followed by osteophyte formation of the L7-S1 end plates and articular processes (Chambers, 1989). The syndrome is characterized by stenosis of the spinal canal from vertebral subluxation and/or stenotic intervertebral foramina.

*Diagnosis:* A diagnosis of lumbosacral syndrome is suspected from the neurological examination. Definitive diagnosis of degenerative LSS is difficult because no one test has 100% specificity and sensitivity, causing false positives and negatives. Diagnostic procedures to test for degenerative LSS include electrophysiology, survey radiography, myelography, epidurography, discography, CT and MRI.

EMG is used to evaluate for spontaneous activity (fibrillation and positive sharp waves) in the following muscle groups: limbs; lumbosacral and caudal paraspinal; external anal sphincter; and pelvic diaphragm muscles (Oliver *et al.*, 1978; Sisson *et al.*, 1989). Abnormal electrodiagnostic findings support pathology but negative findings do not rule out lumbosacral pathology. Sciatic nerve conduction studies also may be abnormal.

Survey radiography is useful to rule out other causes of cauda equina syndrome. Abnormal findings associated with degenerative LSS include: osteochondrosis of

the sacral end plate (Lang *et al.*, 1992; Hanna, 2001); transitional vertebrae (Morgan *et al.*, 1993); spondylosis (Wright, 1980); subluxation; sclerosis of the end plates; and bony proliferation of the articular processes. Transitional vertebrae have been identified as a predisposing cause of cauda equina syndrome in German Shepherd Dogs (Morgan *et al.*, 1993). Stress radiography (extension and flexion) has been used to identify underlying instability of the lumbosacral (LS) junction.

Myelography is a contrast procedure mainly used to rule out other causes of compressive myelopathies cranial to L4. Although it may be used to assess the lumbosacral region (Lang, 1988), due to early termination of the dural sac, the contrast column may not cross the LS junction in large breed dogs.

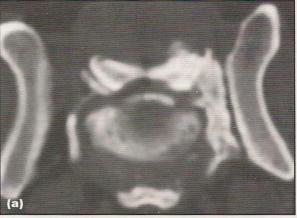
Epidurography is a contrast procedure used to evaluate for dynamic and compressive LS lesions (Selcer et al., 1988). Injection of contrast medium should occur between S3 and Cd1, or more caudally. Radiographic exposure should occur during the contrast injection - lateral views using neutral, flexed and extended positions as well as ventrodorsal views should be obtained (see Chapter 5). A normal epidurogram occurs when contrast medium fills the epidural space and the ventral column is visible on the vertebral canal. Abnormal findings include narrowing, elevation, deviation or obstruction of the contrast column involving >50% of the vertebral canal diameter (Figure 18.8). Involvement of <50% of the canal diameter makes the diagnosis less certain. Diagnostic sensitivities vary between 75 and 80%.



18.8 Abnormal epidurogram showing >50% compression of the epidural space (arrowed).

Discography is a contrast procedure used to evaluate for evidence of disc protrusion at the LS space (Sisson *et al.*, 1992; Barthez *et al.*, 1994). The technique consists of injecting contrast medium into the nucleus pulposus region of the disc (see Chapter 5).

CT has the advantages of better soft tissue and bone resolution (Jones *et al.*, 1995). Cross-sectional, dorsal and sagittal images provide determination of lesion extent (Figure 18.9). The articular processes, intervertebral discs and foramina are evaluated. The procedure should be performed prior to injection of any contrast medium into the vertebral canal or subarachnoid space. Abnormalities detected by CT include loss of epidural fat, increased soft tissue opacity in the intervertebral foramen, bulging of the intervertebral disc, thecal sac displacement, spondylosis, narrowed vertebral canal, thickened articular processes and osteophyte formation of articular processes in the intervertebral foramen (Jones *et al.*, 1996, 1999). CT tends to have a higher

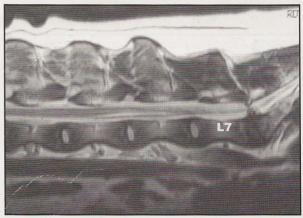




18.9
CT images of degenerative lumbosacral stenosis provide clear soft tissue and bone resolution.
(a) Cross-sectional view. (b) Sagittal view showing dramatic disc protrusion.

sensitivity for diagnosis of degenerative LSS than does either epidurography or discography.

MRI is superior to CT with regard to soft tissue definition (de Haan *et al.*, 1993). The spinal cord, CSF, intervertebral discs, ligaments and nerve roots can be directly visualized (Figure 18.10). MRI can provide early recognition of intervertebral disc degeneration. Disadvantages of this technique include longer imaging times, greater expense and less availability.



Sagittal T2-weighted MR image of a 9-year-old Newfoundland with lumbosacral pain, a limp tail and urinary incontinence. There is marked ventral compression of the nerve roots due to disc protrusion, in addition to dorsal compression due to ligamentous hypertrophy at L7–S1. There is loss of the usual hyperdense signal in the degenerative L7–S1 disc.

*Treatment and prognosis:* Degenerative LSS is managed conservatively or surgically.

Conservative management: Indications for conservative management include the first episode of clinical signs or intermittent pain. Management consists of strict confinement for 8–14 weeks, anti-inflammatory medication using low-dose prednisolone or non-steroidal anti-inflammatory drugs (NSAIDs) and weight loss. The recovery rate for conservative management is between 24 and 50% (De Risio 2001).

Surgical management: Indications for surgical management include failure of conservative management, severe pain and severe neurological deficits (in particular incontinence). Surgical techniques include decompression and excision of proliferative tissue, and fixation and fusion of the LS junction. Surgical decompression is the most common treatment (Chambers *et al.*, 1988).

Dorsal laminectomy allows decompression and visualization of the cauda equina. The nerve roots can be retracted laterally for visualization of the disc for annular fenestration. A foraminotomy can be performed using a bone curette or pneumatic drill. It is important to salvage the articular processes because sacrifice of these structures may destabilize the LS joint. Short-term success using a decompressive laminectomy procedure ranges from 73 to 93% (Chambers *et al.*, 1988; Danielsson and Sjostrom, 1999; De Risio *et al.*, 2001).

Stabilization procedures include distraction—fusion, fusion, lag screw of facets and Kirschner techniques (Slocum and Devine, 1986, 1989; Auger *et al.* 2000). The purpose of the distraction—fusion technique is to enlarge the collapsed disc space and foramina. The lag screw technique has the potential to further weaken and fracture the articular processes — if there is potential for instability, the author prefers placement of threaded mandibular pins into the vertebral bodies of L7 and the sacrum, and using methylmethacrylate bone cement to bridge the pins. Long-term outcome still remains to be determined with this procedure.

The most crucial aspect to postoperative care is strict cage confinement for 8–12 weeks and a gradual return to fitness. Additionally, bladder management involves proper monitoring of bladder emptying to avoid urinary tract infections (UTIs).

If clinical signs resolve with surgery then prognosis is fair to good. Recurrence rates for degenerative LSS vary between 3% and 18% in the working dog (Danielsson *et al.*, 1999; De Risio *et al.*, 2001). Dogs with severe neurological deficits and urinary and faecal incontinence for more than a few weeks prior to surgery have a guarded to poor prognosis (De Risio *et al.*, 2000).

## Intervertebral disc disease

Hansen type II intervertebral disc herniation is an important component of degenerative LSS (see above). Type I herniations of mineralized disc material are much more unusual at this site but can occur (see Chapters 14 and 15 for a description of type I disc herniations).

# Anomalous diseases

#### Transitional vertebrae

Transitional vertebrae are relatively common at the LS junction and have been shown to predispose to degenerative LSS in German Shepherd Dogs (see above).

#### Spina bifida

Clinical signs: Spina bifida occurs most commonly in the caudal lumbar region but can occur in the thoracic region (Figure 18.11). Physical examination at the lesion site may reveal abnormal directions of hair growth, a skin dimple or an open tract draining CSF. More severe lesions have protruding cysts or open regions of the spinal canal (Fingeroth et al., 1989). Clinical signs are reflective of a myelopathy from the L4 to S3 spinal cord region. Severity of clinical signs varies with the degree of meningeal and spinal cord involvement. Tethered cord syndrome can contribute to the progression of the condition as the animal matures. Spinal cord tethering is defined as caudal displacement of the spinal cord associated with one or more abnormality (e.g. a meningocele). Affected animals may have ambulatory difficulties and faecal or urinary incontinence. Animals with spina bifida occulta usually have no neurological deficits related to the malformation.



18.11

Spina bifida and a butterfly vertebra at L4 (arrowed) in a young, male Bulldog.

Pathogenesis: Spina bifida is characterized by failure of the vertebral arches to fuse, with or without protrusion of the spinal cord and meninges (Bailey and Morgan, 1992; Kroll and Constantinescu, 1994). Spina bifida occulta is characterized by an absence of the vertebral arches, with normal spinal cord and meninges. More severe forms include protrusion of meninges (meningocele) and/or spinal cord (meningomyelocele) through the defect (see Chapter 15). Spina bifida occurs in both dogs and cats and there is a high incidence in the Bulldog and Manx cats (see Sacrocaudal dysgenesis), which may suggest a heritable cause (Kitchen et al. 1972; Wilson, 1982).

Teratogenic compounds, nutritional deficiencies and environmental factors may be associated with

spina bifida (Khera, 1973; Scott *et al.*, 1975). A combination of genetic predisposition and environmental factors may also be responsible.

*Diagnosis:* Survey spinal radiography can detect failure of the dorsal spinous processes to fuse, especially on the ventrodorsal view (see Figure 18.11). Spina bifida is usually an incidental finding. Myelography can detect a meningocele. MRI may further delineate other spinal cord abnormalities.

Treatment and prognosis: Treatment of spina bifida occulta is rarely attempted. Meningocele can be amenable to surgery but associated spinal cord abnormalities need to be taken into account. The filum terminale is severed to promote subsequent release of the tether (Fingeroth et al., 1989; Plummer et al., 1993). Prognosis is considered good if there are minimal clinical signs and spina bifida is the only abnormality. It is poor if the animal is faecally and urinary incontinent with absent perineal sensation.

# Sacrocaudal dysgenesis in Manx cats

Clinical signs: Affected Manx cats have a 'bunny-hopping' gait but can manifest more severe signs of paresis and urinary and faecal incontinence. Sensory abnormalities include hypoaesthesia or analgesia of the perineal region. Malformations of the sacral or caudal vertebrae may be palpable. A dimple in the skin may indicate a meningocele. Innervation of the anus and bladder is often absent causing urinary and faecal incontinence. The urinary bladder may be easily expressible. Postural reactions and spinal reflexes are decreased in the pelvic limbs. A fistulous meningocele can cause hypochloraemia and hyponatraemia subsequent to CSF drainage (Hall et al., 1988).

**Pathogenesis:** The autosomal dominant trait in Manx cats lends itself to the absence of a tail but also to numerous sacral related anomalies (Kitchen *et al.*, 1972; Yeatts, 1998) The Manx gene is considered semi-lethal, with homozygotes not surviving. Manx tail types are classified into four phenotypic groups (Davidson, 1986):

- Rumpy (no caudal vertebrae)
- Rumpy-riser (several caudal vertebrae fused)
- · Stumpy (several caudal mobile vertebrae) and
- · Longie ('normal' tail).

Neurological deficits are often found in the rumpy phenotype. The 'rumpies' can exhibit an absence of sacral and even lumbar vertebrae with increased associated spinal cord dysgenesis. Deficits sometimes develop over weeks to months as the cat matures. These deficits are due to the failure of cranial migration; or 'tethering' of the spinal cord as the caudal end of the spinal cord and dural sac fail to stretch normally (Dorn and Joiner, 1976; Plummer et al., 1993). Spina bifida is usually present. Other concurrent spinal cord abnormalities include meningocele, myelomeningocele, syringomyelia, diastematomyelia and spinal dysraphism (see Chapter 15).

**Diagnosis:** Survey radiography of the lumbosacral spine will demonstrate bony defects. The spinal defects can be detected by CT, myelography or MRI. Electrophysiology can be used to confirm the extent of denervation.

Treatment and prognosis: Early surgical intervention is recommended if signs of spinal cord tethering are suspected. The filum terminale is transected or freed from the abnormal meningeal attachments. Any fistulous tract that exists between the skin and subarachnoid space should be dissected free and completely resected to prevent infection and loss of CSF (Dorn and Joiner, 1976; Plummer et al., 1993). The bladder needs to be frequently expressed. Bladder infections are treated with appropriate antibiotics. When the clinical signs are due to absent or severely affected nerve supply the prognosis for functional improvement is grave. If clinical signs are secondary to spinal cord tethering the prognosis can be good with early surgical intervention.

# Neoplastic diseases

See Chapter 15 for a description of all neoplastic diseases that affect the spinal cord and Chapter 16 for a description of peripheral nerve sheath tumours. Tumours specific to the cauda equina are addressed below.

#### Chordoma

Chordomas have been recognized in humans, ferrets, rats, mink, cats and dogs. Most chordomas develop in the sacrococcygeal region but can also occur in other parts of the CNS (Williams et al., 1993; Pease et al., 2002). Chordomas most likely originate from notochordal remnants. The notochord normally remains as the nucleus pulposus within the intervertebral disc. Residual notochord outside the intervertebral discs lies close to the base of the skull and the sacrum. Chordomas may occur at the site of a previous tail docking (Munday et al., 2003). Tail amputation may displace the notochord cells, which subsequently undergo neoplastic transformation. Chordomas are slow growing with low metastatic potential. Routine histology of an excisional biopsy sample allows for a presumptive diagnosis based on the characteristic histological and immunohistochemical appearance. Prognosis is good with complete surgical excision.

# Lipomas

Intradural lipomas are a recognized syndrome in humans with tethered spinal cord syndrome. There is one report of an intradural lipoma in a young Manx-type cat with associated with a meningocele (Plummer *et al.*, 1993).

# Inflammatory diseases

The sacrococcygeal nerves can be involved in multifocal or diffuse inflammatory diseases that are described in Chapter 10. The involvement of these nerves may imply a poor prognosis for the patient due to the possibility of permanent incontinence. Specific inflammatory diseases of this localization are discussed below.

#### Tail abscessation

Clinical signs: Abscessation of the tail causes severe pain, paresis or paralysis of the tail and, depending on the extent of the lesion, can spread to involve the sacral and sciatic nerves causing incontinence and paraparesis. A wound is usually visible on the tail.

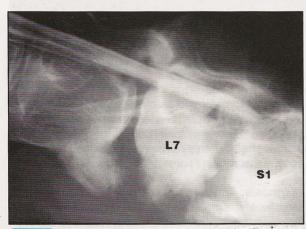
**Pathogenesis:** Trauma, bite wounds or surgery to the rump may disrupt innervation to the tail, anus and bladder (Ndikuwera *et al.*, 1987). A focal bacterial abscess develops in the area of the tail head or involves the cauda equina.

**Diagnosis:** Cytology and culture of abscess confirm the diagnosis.

**Treatment and prognosis:** Antibiotics are selected based upon culture and sensitivity and should be administered for 6–8 weeks. Depending on the response to therapy and on the severity of the neurological deficits, a dorsal laminectomy may be necessary for decompression and removal of the abscess. Prognosis for recovery can be good but is dependent on the severity of the neurological deficits at the time of presentation.

## Discospondylitis

Discospondylitis refers to infection (usually bacterial) of the intervertebral disc and adjacent vertebral end plates. The L7–S1 disc space and vertebrae are regularly involved (Figure 18.12) causing severe LS pain and cauda equina syndrome (see Chapter 13 for more details).



Discospondylitis affecting the L7–S1 disc space and associated vertebrae.

# **Idiopathic diseases**

# Feline dysautonomia

Dysautonomia in cats was initially described by Key and Gaskell 1982 (Griffiths *et al.*, 1982; Sharp *et al.*, 1984). The incidence of this disease in the UK and Scandinavia between 1982 and 1986 reached near-epidemic proportions; the frequency has since spontaneously decreased. The disease has been rarely reported in the USA.

Clinical signs: There is no breed, gender, age or environmental predisposition in cats affected by dysautonomia. Onset of clinical signs is acute or insidious. The most consistent clinical findings include anorexia, weight loss and depression (Rochlitz, 1984). Common clinical signs reflective of autonomic dysfunction include dilated pupils, constipation, dry mucous membranes, reduced tear production, regurgitation and protruded third eyelid.

**Pathogenesis:** The aetiology of feline dysautonomia is unknown despite extensive efforts to establish an association. The disease is histologically characterized by chromatolysis of the sympathetic and parasympathetic ganglia with less severe changes in the ventral horn grey matter and motor nuclei of the oculomotor, trigeminal, facial, vagus and hypoglossal nerves (Sharp *et al.*, 1984).

Diagnosis: A diagnosis is made based on clinical signs in fulminant cases of dysautonomia. An accurate diagnosis is obtained based on radiography, ocular examination and pharmacological testing. Radiography may detect megaoesophagus or signs of gastrointestinal stasis. Ophthalmic examination reveals mid-range to dilated pupils, a prolapsed nictitating membrane and a reduced Schirmer tear test (Figure 18.13). In a study by Guilford et al. (1988) a dilute (0.1%) pilocarpine solution (a direct-acting cholinergic agonist) was applied topically to one eye of an affected cat and to one eye of a normal cat. The pupil of the affected cat produced a miotic response within 20-40 minutes suggesting denervation supersensitivity. The ocular signs combined with signs of generalized parasympathetic and sympathetic failure are highly suggestive of feline dysautonomia. Definitive diagnosis is obtained by histological evaluation of the autonomic ganglia (Kelly, 1987).



18.13 Ophthalmic examination of a domestic short-haired cat with feline dysautonomia. Note the prolapsed nictitating membranes and dilated pupil of the right eye. (Courtesy of Dr Dennis O'Brien, University of Missouri)

**Treatment and prognosis:** Management of feline dysautonomia is by supportive care. Adequate nutrition is maintained by alimentary or parenteral nutrition methods. Artificial tears and nebulization are used to

reduce irritation from dried mucous membranes. Pilocarpine is used to ameliorate ocular abnormalities. Low-dose bethanecol chloride may aid in urination (see Figure 18.22). Antiemetics such as metoclopramide may offer some relief in cats with severe vomiting. Supportive treatment offers palliation of clinical signs and time for some cats to recover neurological function (McNulty *et al.*, 1999).

Owners should be informed about the length of convalescence and the amount of care required. Recovery usually begins several months after onset of clinical signs and may take a year or longer. Some animals never regain function. Cats that are more severely affected have longer and less complete recoveries. Complications such as untreatable vomiting and urinary incontinence may necessitate euthanasia.

# Canine dysautonomia

Clinical signs: Onset of clinical signs is considered acute and progressive. Clinical signs reflect severe autonomic nervous system damage (Longshore et al., 1996; Harkin et al., 2002). Common clinical signs include depression, dilated or mid-range pupils with no pupillary light reflex, dysuria, dry mucous membranes, gastrointestinal signs (dysphagia, regurgitation or vomiting), elevated third-eyelids and decreased anal reflex (Figure 18.14). The severity and type of clinical signs vary in dogs affected by dysautonomia.



18.14 A young male mixed-breed dog with canine dysautonomia demonstrating a dilated anus. (Courtesy Dr Dennis O'Brien, University of Missouri)

Pathogenesis: Canine dysautonomia was first reported in the UK in 1983 (Rochlitz and Bennett, 1983). The aetiology of the disease is unknown but is characterized by widespread degeneration of the neurons and ganglia of the autonomic nervous system (Pollin and Sullivan, 1986; Pollin and Griffiths, 1992). Progressive dysfunction of the gastrointestinal, urinary and other autonomic dependent systems leads to severe physical deterioration and death. In the USA, dogs are the predominantly affected species and most cases described in the literature have been from the mid-western states (Berghaus et al., 2002). Risk factors have included a rural environment and dogs spending more than 50% of their time outdoors (Berghaus et

al., 2001). Seasonal risk is highest between February and April (Berghaus et al., 2001; Harkin et al., 2002). The disease usually affects young dogs.

*Diagnosis:* A diagnosis is suspected based on clinical signs. Pharmacological testing can be performed in live animals to provide supportive evidence for a diagnosis. Responses to ocular instillation of dilute (0.05–0.1%) pilocarpine drops and subcutaneous injection of low doses of bethanecol chloride (0.04 mg/kg of bodyweight) have been used to rule out the inability of the iris and detrusor muscles to contract and thus suggest denervation hypersensitivity (Longshore *et al.*, 1996). The preferred way to confirm a diagnosis of dysautonomia is by histological examination of the autonomic ganglia.

Radiographic findings supportive of dysautonomia include aspiration pneumonia, megaoesophagus or a distended stomach, small bowel or urinary bladder (Detweiler *et al.*, 2001).

**Treatment and prognosis:** Treatment is considered palliative. Autonomic dysfunction can be treated specifically with low-dose pilocarpine and bethanecol chloride to improve signs of dysuria; however, over time response to therapy decreases. The prognosis for dysautonomia is grave unless dogs are mildly affected with dysuria and do not have digestive tract signs (Harkin *et al.*, 2002).

#### Traumatic diseases

Fractures and luxations of the caudal lumbar and sacral vertebrae

*Clinical signs:* Luxations at L7/S1 can cause severe compression of the L7 nerve roots resulting in severe pain and a dramatic nerve root signature. Neurological signs reflect damage to the sciatic, sacral and coccygeal nerves.

**Pathogenesis:** Fractures of L6 and L7 are common with the caudal part of the vertebrae often cranioventrally displaced. Since the spinal cord terminates cranial to these vertebrae only nerve roots (the cauda equina) occupy this region (Turner, 1987).

**Diagnosis:** The diagnosis is based on radiographic findings. Myelography or CT/MRI may be necessary to further establish spinal cord compression or damage. Spinal instability is assessed based upon the degree of vertebral damage (Shires *et al.*, 1991) (see Chapter 19).

**Treatment and prognosis:** Fractions and luxations are managed either medically or surgically.

Conservative management: For information on the conservative treatment of fractures and luxations of the caudal lumbar and sacral vertebrae see Chapter 15.

Surgical management: Treatment usually requires surgical stabilization. Several surgical techniques of inter-

nal spinal fixation for management of caudal lumbar vertebral fractures have been reported (Swaim, 1971; Blass and Seirn, 1984; Ullman and Boudrieau, 1993; Bagley et al., 2000). Techniques often involve pins or screws and polymethylmethacrylate (PMMA) (Beaver et al., 1996; Sturges and LeCouteur, 2003) (Figure 18.15). Advantages of using screws or pins with PMMA when compared with other techniques, such as spinal stapling, are minimized tissue dissection and shorter segments of the vertebral column being immobilized. A dorsal laminectomy may also be indicated to evaluate the cauda equina for compression and nerve integrity. External spinal fixation has been used successfully to facilitate stability and healing (Shores et al., 1989; Lanz et al., 2000).

Further postoperative management focuses on avoiding complications of recumbency by methods of physical therapy and bladder care (Bagley *et al.*, 2000; Tefend and Dewey, 2003) (see Chapter 24).



18.15 A lateral plain film radiograph demonstrating use of polymethylmethacrylate and Steinmann pins to stabilize an L7 fracture/luxation.

Although considerable displacement may occur the results of stabilization tend to be good if deep pain perception is intact in the tail and lateral digits of the pelvic limbs, and perineal sensation is present (as an indicator of injury severity to the sacral segments). Transection of the sacral nerves usually results in permanent faecal and urinary incontinence.

## Sacral fractures

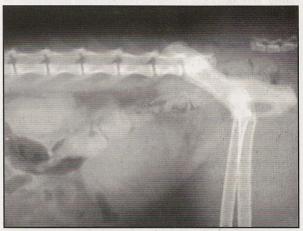
Sacral fractures occur frequently after vehicular-related trauma. The sacrum contains the nerve roots that contribute to the pelvic and pudendal nerves. The coccygeal nerves also course through the sacral canal. Sacral fractures may result in faecal and urinary incontinence and neurological deficits to the pelvic limbs, perineum and tail. Fractures medial to the sacral foramina (axial) cause significantly more severe deficits but prognosis for recovery does not differ from fractures lateral (abaxial) to the foramina (Kuntz et al., 1995). Axial sacral fractures most frequently result in urinary and/or faecal incontinence, loss of perineal sensation and tail analgesia. Abaxial fractures are more frequently associated with pelvic limb deficits.

# Sacrococcygeal fracture/luxation and tail avulsions

Clinical signs: Sacroccoccygeal (also known as sacrocaudal) fracture-luxations and tail avulsions occur most commonly in cats (Smeak and Olmstead, 1985). Affected cats usually have a paralysed tail with complete anaesthesia. Depending upon the extent of the injury, these cats also have urinary and faecal incontinence and partial loss of sciatic nerve function.

**Pathogenesis:** The amount of displacement following sacrococcygeal fracture and/or luxation varies considerably. Damage to the nerve roots and associated spinal cord is caused by traction resulting in damage to the more cranial lumbosacral intumescence.

**Diagnosis:** The diagnosis is made from the history, clinical signs and radiographic confirmation (Figure 18.16). In rare instances there is no evidence of a fracture or luxation but the signs and history are consistent with a traction injury.



Radiography was used to confirm diagnosis of a complete coccygeal vertebral luxation in a cat with avulsion of the tail.

**Treatment and prognosis:** Fractures of the coccygeal vertebrae are stabilized as soon as possible to prevent further traction injury to the lumbosacral spinal cord. If stabilization of the coccygeal vertebrae is not possible, tail amputation is a viable option. The bladder must be manually expressed or catheterized until function is regained (see Chapter 24).

The prognosis for return of urinary continence is good if anal tone and perineal sensation are present on initial examination. Cats that do not become continent within one month usually fail to regain urinary function (Smeak and Olmstead, 1985).

#### Vascular diseases

#### Coccygeal muscle injury

Clinical signs: Coccygeal muscle injury or 'limber tail' is a term for a condition seen in hunting dogs (Steiss et al., 1999). The breeds commonly affected are Pointers and Labrador Retrievers but it is seen in

other breeds. Tail carriage is affected to varying degrees and can appear flaccid. The hair on the proximal tail is raised and dogs may resent palpation. Dogs exhibiting this tail carriage are usually withdrawn from competition.

Pathogenesis: Prolonged cage transport, underconditioning or overexertion, and changes in climate are factors known to predispose to this condition. Pathology is associated with ischaemic damage to the coccygeal muscles confirmed by histology. It is suggested that limber tail mimics compartment syndrome in humans. Compartment syndrome is characterized by pain, swelling, lack of arterial pulses and paralysis occurring in muscle groups that are adjacent to bone and enclosed by thick fascial layers.

Diagnosis: The diagnosis is based upon history and clinical signs, with trauma as a primary differential. Diagnosis can be substantiated by detecting an elevated creatine kinase (CK) serum concentration if examined early in onset of clinical signs, or by thermography. Biopsy of tail is not recommended because the muscle groups are small and nerves are in close proximity. Abnormal spontaneous activity has been detected on EMG.

Treatment and prognosis: Most dogs recover spontaneously within a few days to weeks. Anti-inflammatory drugs administered at onset of clinical signs may hasten the recovery process. Prognosis is good and less than half the cases have been known to recur.

#### Fibrocartilaginous embolism (FCE)

Embolization of fibrocartilage into the spinal cord vasculature commonly affects the lumbosacral intumescence. When the embolic episode is limited to the sacral spinal cord it causes mild paresis with sciatic deficits, and severe urinary and faecal incontinence, with variable involvement of the tail. This syndrome of embolization of nuclear disc material is described in full in Chapters 14 and 15.

#### Normal and abnormal micturition

The micturition process includes both the storage and emptying phases of bladder function; whereas, urination refers to just the voiding phase. Normal bladder and urethral function is required for micturition to occur. The normal micturition process includes passive filling of the bladder, which uses the mechanisms that maintain continence; and bladder emptying, which requires relaxation of the sphincters in conjunction with a coordinated voluntary bladder contraction (de Groat and Booth, 1980). This process is under control of the CNS, which integrates the autonomic and somatic nervous systems.

# Functional neuroanatomy of micturition

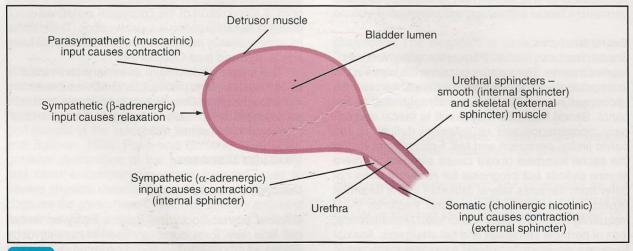
A basic knowledge of the anatomy and physiology of micturition is necessary to evaluate and manage micturition disorders (O'Brien, 1990; de Groat, 1993; Oliver, 1997). The lower urinary tract may be thought of as consisting of a detrusor (bladder) muscle (smooth muscle) and two sphincters: the internal smooth muscle sphincter at the proximal urethra and bladder neck; and the external skeletal muscle sphincter that encompasses the membranous urethra (Augsburger et al., 1993). These structures are innervated by the autonomic (smooth muscle) and somatic nervous systems (skeletal muscle).

#### **Detrusor muscle innervation**

β-adrenergic (hypogastric nerve: L2-L5 spinal cord segments in the cat. L1-L4 in the dog) and cholinergic (muscarinic: pelvic nerve: spinal cord segments S1-S3) receptors coordinate bladder filling and evacuation, respectively (Figure 18.17).

Sensory receptors in the wall of the bladder include:

- Stretch receptors innervated by afferent fibres of the pelvic nerve
- Pain receptors innervated by afferent fibres transmitted via the pelvic and hypogastric nerves but primarily through the hypogastric nerve.



18.17

Schematic anatomy of the bladder and urethra

#### **Urethral innervation**

The smooth muscle portion of the urethra is innervated by the hypogastric nerve ( $\alpha$ -adrenergic receptors) causing constriction and internal sphincter closure.

The skeletal muscle portion of the urethra is innervated by the pudendal nerve (nicotinic cholinergic receptors) whose cell bodies are in the sacral spinal cord (S1–S2).

There also are sensory receptors in the wall of the urethra that detect stretch, pain and urine flow. These receptors are primarily innervated by afferent fibres of the pudendal nerve, although, nociceptors are innervated by afferent fibres of the hypogastric nerve.

# **Central integration**

The brainstem micturition centre in the pons receives sensory input from the bladder stretch and pain receptors. The centre is responsible for coordinating sphincter relaxation with detrusor contraction.

The cerebral cortex, basal ganglia, thalamus and cerebellum have an inhibitory influence over the process of micturition and are ultimately responsible for its voluntary control.

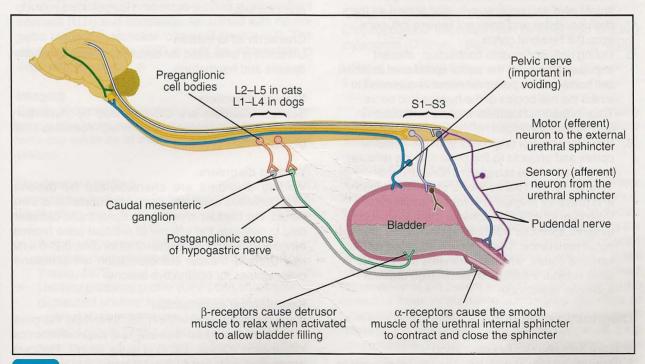
# Storage phase of micturition

- During storage the detrusor muscle receives its innervation from the sympathetic nervous system (SNS) (β-adrenergic receptors) via the hypogastric nerve (Oliver, et al., 1969; Purinton and Oliver, 1979) (Figure 18.18). The SNS facilitates urine storage via bladder wall relaxation by the influence of norepinephrine (noradrenaline) on the β-adrenergic receptors.
- The bladder trigone (neck) and proximal smooth muscle of the urethra receive innervation from SNS also via the hypogastric nerve, mediated via

- $\alpha$ -adrenergic receptors producing sphincter contraction.
- 3. The striated muscle of the urethra receives its innervation from the somatic nervous system via the pudendal nerve with acetylcholine binding to nicotinic receptors (Bradley et al., 1973). The pudendal nerve function during the storage phase is to provide tonic sphincter contraction.
- 4. Supraspinal organization of the micturition reflex (micturition centre in the pons) supplies descending pathways to mediate sympathetic, parasympathetic and somatic activities during storage and voiding phases of urination. Urine storage involves coordinated relaxation of the detrusor muscle and contraction of the sphincter muscles. SNS activities predominate an easy way to commit this concept to memory is that the SNS provides the 'fight or flight' mechanism and 'when you are fleeing you shouldn't be peeing'.
- 5. As urine volume and bladder pressure increase, stretch receptors in the urinary bladder are activated and project afferent sensory information to the brainstem and cerebral cortex via the pelvic nerve and spinothalamic tracts. Painful stimuli within the bladder mucosa are transmitted via the hypogastric nerve and associated sympathetic pathways.

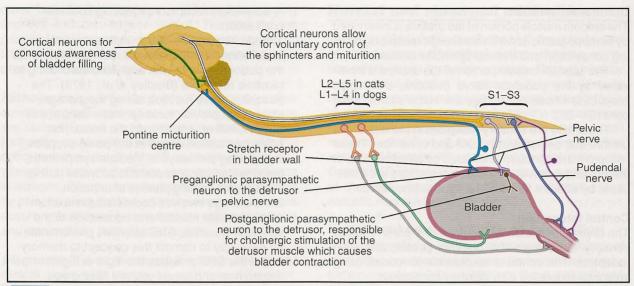
# Voiding phase of micturition

1. During voiding the detrusor muscle receives its innervation from the parasympathetic nervous system (PNS; cholinergic receptors) via the pelvic nerve (Oliver *et al.*, 1969; Purinton and Oliver, 1979) (Figure 18.19). The pelvic nerve facilitates detrusor contraction through the action



18.18

Schematic overview of the neuroanatomy of the storage phase of micturition.



**18.19** Schematic overview of the neuroanatomy of the voiding phase of micturition.

- of the neurotransmitter, acetylcholine, on muscarinic cholinergic receptors.
- 2. Urine voiding involves coordinated contraction of the detrusor muscle and relaxation of the sphincter muscles.
- When stretch receptors within the bladder wall are stimulated, afferent impulses are transmitted via the pelvic nerve to the sacral spinal cord and ascend to the pontine reticular formation in the brainstem (micturition centre) and to the cerebral cortex.
- 4. The micturition centre coordinates urethral sphincter relaxation and initiates and sustains detrusor contraction during voiding. Coordination of urination from the reflex arc involving the spinal cord and brainstem is also known as the detrusor reflex and does not require influence from the cerebral cortex.
- 5. During detrusor muscle contraction, afferent impulses also enter the sacral spinal cord to inhibit cell bodies of the pudendal nerve and ascend to inhibit the cell bodies of the hypogastric nerve. Thus initiation of detrusor muscle contraction in turn inhibits contraction of the urethral sphincters.
- 6. Voluntary control originates from the cerebral cortex and projects to the pons and the reticular spinal tract of the spinal cord (Bradley and Timms, 1974). This control is primarily inhibitory and prevents involuntary bladder contraction. Voluntary inhibition of somatic discharge to the external sphincter additionally decreases urethral outlet resistance. The pons is modulated by the cerebral cortex, which coordinates this activity to allow normal voiding with decreased urethral sphincter resistance.

# Diagnostic evaluation

# History and physical examination

A thorough history and physical examination need to be performed in all cases of micturition dysfunction (Lane, 2000, 2003). The external genitalia are examined for masses, abnormal conformation and urine scalding. In cases of urinary incontinence, physical examination will reveal evidence of urine soiling around the genitalia and caudal thigh region. A pool of urine may be left where the animal has been lying down or sleeping. Abdominal palpation may reveal bladder size, wall thickness and presence of any masses. In cases of urinary retention the bladder is often enlarged. The bladder is often large, firm and difficult to express with upper motor neuron (UMN) lesions; while large, flaccid and easily (but incompletely) expressed with LMN lesions. Manual expression of the bladder can assess urethral sphincter tone. Digital rectal palpation will assess the pelvic urethra and prostate.

#### Character of urination

Urination is evaluated for duration, stream character, dysuria and haematuria.

# Storage disorders

Storage disorders are characterized by involuntary leakage of small amounts of urine with normal to small bladder size.

# Voiding disorders

Voiding disorders are characterized by dysuria, stranguria and urine retention. After urination is completed, the bladder should be palpated and catheterized to evaluate the volume of residual urine (normal range is <10 ml for dogs and <2 ml for cats; 0.2–0.4 ml/kg). Urethral bladder catheterization will simultaneously assess for obstructive lesions.

## **Neurological examination**

A neurological examination will ascertain the presence of neurological disease and neuroanatomical localization (Oliver, 1997) (Figure 18.20). Reflexes associated with the pudendal nerve are especially important to evaluate.

Lesion localization	Conscious voiding attempts	Bladder expression/ size	Residual urine	Perineal reflex	Type of micturition dysfunction
Cerebral cortex to brainstem	Absent	Difficult/small	Small	Present	Inappropriate urination
Cerebellum	Normal; increased frequency	Difficult/small	Small	Present	Detrusor hyperreflexia
Brainstem to L7	Absent; dyssynergia	Difficult/large; tapering stream; small spurts of urination	Large-moderate amount	Present	Failure to eliminate urine; reflex incontinence; overflow incontinence
Sacral spinal cord	Absent; may attempt but limited success	Easy; leakage; may have some resistance/large	Large amount	Reduced to absent	Urethral incompetence; detrusor atony; overflow incontinence
Disruption of tight junctions to the detrusor muscle	Absent	Some resistance; bladder is flaccid/ large	Large amount	Present	Overflow incontinence

18.20

Localization and clinical signs of micturition dysfunction.

- Anal sphincter tone is evaluated by digital rectal examination.
- The bulbocavernosus reflex is a sharp contraction of the anal sphincter and tail in response to a squeeze of the bulb of the penis or clitoris.
- The perineal reflex is a contraction of the anal sphincter in response to a pinch of the perineal region and sensory perception is simultaneously evaluated
- Urethral sphincter tone is assessed by manual bladder expression.

# Urinalysis and urine culture

Urinalysis and urine culture are performed to identify obvious pathological processes such as a urinary tract infection (UTI) and neoplasia. An animal with neurogenic bladder dysfunction often will have a UTI. The urine specific gravity (SG) should be informative in dogs with polyuria.

#### **Imaging**

Survey abdominal radiography, ultrasonography, contrast cystography and urethrography will further delineate any evidence of mass or anatomical obstructive lesions.

#### **Urodynamic testing**

Urodynamic testing can further assist with anatomical localization.

- A cystometrogram (CMG) monitors bladder pressure during filling and emptying (Oliver and Young, 1973).
- Urethral pressure profile (UPP) can assess for decreased urethral tone (decreased mean urethral closure pressures) and functional urethral length (Rosin et al., 1980). The UPP measures urethral pressure at points along the urethral length using a small catheter that is slowly withdrawn along the urethra and

- connected to a pressure transducer.
- Leak point pressure testing is a functional technique used to simulate urethral compliance associated with an external abdominal press (Rawlings et al., 1999).
- EMG assessment of pudendal nerve function using a recording electrode on the perineum and external sphincter (Bradley et al., 1975).

Although urodynamic testing can be performed at most university-based referral hospitals, similar information can often be acquired by closely observing the animal during urination, measuring residual volume and determining any resistance during catheterization.

# Causes of micturition dysfunction

Disturbances of micturition can be classified into two categories (O'Brien, 1988; Oliver, 1997; Lane, 2000):

- · Failure to store urine
- · Failure to eliminate urine.

Structural and neurogenic lesions that primarily and secondarily affect the bladder and urethra cause abnormalities in micturition.

# Failure to store urine

Failure to store urine can result from either urinary bladder dysfunction or urethral sphincter incompetence. Incontinence must be distinguished from inappropriate urination since both abnormalities appear similar to the owner. Inappropriate urination is the act of voiding urine at the wrong time and in the wrong place but it is still under voluntary control of the animal. History and direct observation of the patient will distinguish inappropriate urination from incontinence. Underlying disorders of inappropriate urination in dogs include senility, forebrain disease and lack of willingness and difficulty in reaching an acceptable place to urinate. Forebrain (cerebral cortex and diencephalon) lesions also typically cause behaviour changes and other sensory and motor deficits.

Bladder storage dysfunction: Bladder storage dysfunction relates to poor bladder compliance and/or elasticity during the filling phase or involuntary voiding at low bladder volumes and pressures. Urge incontinence is commonly associated with this type of dysfunction. Non-neurogenic causes include UTIs, chronic inflammatory processes, infiltrative disease (neoplasia) and idiopathic hypercontractility. Neurogenic causes of bladder storage dysfunction consist of detrusor hyperreflexic conditions that occur with cerebellar disorders (degenerative, neoplasia, inflammatory/infectious) and chronic UMN spinal cord disease (detrusor-sphincter dyssynergia or overflow incontinence). Overflow incontinence occurs when detrusor pressure exceeds urethral sphincter resistance.

Urethral incompetence: Urethral incompetence is a result of weakened responses of urethral smooth or skeletal muscles that allow urine leakage during the storage phase of micturition. Non-neurogenic causes include UTIs, neoplasms, ectopic ureters, prostate disorders, hormone-responsive urethral incompetence and metabolic disorders. Polyuric disorders secondary to metabolic disturbances can intensify an underlying incontinence problem when an increase in urine volume further stresses an incompetent urethra. Causes for polyuria include renal failure, diabetes insipidus, diabetes mellitus, hypercalcaemia, electrolyte disturbances, hyperadrenocorticism, hypoadrenocorticism, thyroid disorders, hepatic failure, medications (e.g. glucocorticoids, anticonvulsants, diuretics), prostatic abscess and pyometra. Neurogenic causes for urethral incompetence include those disorders affecting the sacral spinal cord (Figure 18.21).

Hormone-responsive urethral incompetence is the most common cause for urethral incompetence especially in bitches. Urine leakage commonly occurs when the animal is at rest, but voluntary control is present when the animal is alert. A strong correlation exists between bodyweight and the incidence of incontinence. The onset of incontinence after spaying varies between immediately and 10 years, with an average of 3 years

after surgery. A diagnosis of hormone-responsive urethral incompetence should be made after all other causes for acquired incontinence have been ruled out.

#### Failure to eliminate urine

Failure to eliminate (urinary retention) can result from either incomplete or absent bladder contraction, or urethral outflow obstruction (anatomic or functional).

Incomplete or absent bladder contraction: The most common cause of voiding dysfunction associated with urinary retention is considered neurogenic failure. UMN dysfunction occurs with lesions between the pons and L7 spinal cord segment. UMN bladder dysfunction is a common sequela to T3–L3 myelopathies. As described above, both the motor and sensory pathways of the detrusor reflex are affected. The bladder becomes large and firm and the urethral sphincter tone is increased. The bladder is difficult to express manually. Secondary overflow incontinence occurs when bladder pressure exceeds urethral pressure.

LMN bladder dysfunction occurs with a lesion in the sacral spinal cord and nerve roots, and/or the pelvic plexus. A lesion in this area will abolish the detrusor reflex. The detrusor muscle becomes flaccid (detrusor atony) as a result of over-distension secondary to absent detrusor contraction, and external sphincter tone is lost. The internal sphincter is innervated by the hypogastric nerve and remains intact. This may actually make bladder expression difficult. Animals with LMN bladder dysfunction also lose their perineal reflex and sensation. Trauma is the most common cause for this dysfunction and other disorders affecting the sacral spinal cord region are listed in Figure 18.21.

Bladder atony from over-distension can result from non-neurogenic or neurogenic causes. Non-neurogenic bladder atony is secondary to urinary obstruction and disruption of the tight junctions of the detrusor myofibres. Over-distention can also result from pain, for example following pelvic fractures, and recumbency. Disorders associated with generalized weakness, such as myopathic, neuropathic and neuromuscular junction

Disease category	Specific diseases			
Degenerative	Compressive myelopathy – intervertebral disc disease, lumbosacral syndrome, lumbosacral stenosis Noncompressive myelopathy – degenerative myelopathy (late stage)			
Anomalous	Sacrocaudal dysgenesis, myelodysplasia, stenosis			
Neoplastic	Primary – osteosarcoma, chondrosarcoma, fibrosarcoma, nerve sheath tumours, meningioma, chordoma Metastatic (common) – prostatic adenocarcinoma, perianal gland adenocarcinoma, lymphoma			
Infectious	Discospondylitis (Staphylococcus intermedius, Brucella canis and Escherichia coli)			
Inflammatory	Immune-mediated peripheral neuropathies; polyradiculoneuritis; myasthenia gravis (detrusor atony, secondary overflow)			
Idiopathic	Dysautonomia			
Traumatic	Lumbosacral luxation; traction spinal cord injury			
Toxic	Botulism			
Vascular	Fibrocartilaginous embolism			

18.21

Sacral spinal cord lesions causing abnormal micturition.

disorders, can also result in over-distention. Finally dysautonomia can primarily present with urinary tract signs – usually an over-distended bladder that is flaccid and easily expressed.

*Urethral obstruction:* The most common cause of outflow obstruction is anatomical blockage of the urethra. Causes include urolithiasis, neoplasia, prostatic disease and urethral inflammation. Urethral catheterization is often difficult.

Functional urethral obstruction results from neurogenic or non-neurogenic causes (Lane, 2003). UMN lesions result in uninhibited urethral sphincter tone and increased urethral resistance, making voiding or manual expression difficult. This condition is often related to detrusor-sphincter dyssynergia (reflex dyssynergia), which refers to loss of coordination between the bladder and sphincter muscles. It is commonly encountered in animals with spinal cord injury (Oliver, 1983; Barsanti et al., 1996). Dyssynergia refers to simultaneous contraction of muscles whose activity is opposite in direction. Mechanisms for dyssynergia of smooth and skeletal muscle sphincters are mediated by loss of the inhibitory reticulospinal pathways (from the micturition centre) to the sympathetic and somatic (pudendal) efferents, respectively. Affected animals usually have large volumes of residual urine primarily as a result of urethral sphincter spasticity.

Cauda equina lesions also can cause uncoordinated sphincter activity that produces dyssynergic-like voiding patterns and urinary retention (Coates, 1999). Non-neurogenic causes of functional urethral obstruction are a related lack of coordination between

18.22

detrusor contraction and urethral relaxation (e.g. idiopathic detrusor-urethral dyssynergia) or an increase in urethral resistance.

#### Treatment of micturition disorders

Successful management of micturition dysfunction depends on proper identification and treatment of the underlying disorder. Disorders of storage and voiding can be with treated either medically or surgically. Some disorders also may have secondary complicating factors such as a UTI. Medical therapies for urethral and bladder disorders are summarized in Figure 18.22. It is important to understand mechanisms of action, side-effects and contraindications of these drugs. The detrusor muscle should not be stimulated to contract unless the bladder is expressed easily manually.

Surgical methods of management are used to treat urethral incompetence in cases that are refractory to medical therapies. Several methods described include mesh and sling procedures, Teflon injections and colposuspension. Cystourethropexy and colposuspension procedures have been performed with variable success (Gregory and Holt, 1994; Rawlings *et al.*, 2000). Colposuspension is a surgical technique that moves the bladder neck from an intrapelvic to an intra-abdominal position and restores continence by increasing pressure transmission to the proximal urethra and bladder neck.

Basic principles need to be followed to prevent bladder overdistension in animals with urinary retention. Intermittent urinary catheterization is often indicated and has a lower risk of inducing a UTI than

Desired effect	Drug	Mechanism of action	Dosage <sup>a</sup>	Side-effects
Stimulate detrusor contraction	Bethanecol chloride	Cholinergic stimulation	2.5–25 mg orally q8h	Increase GI motility; vomiting; diarrhoea; hypersalivation; hypotension; bradycardia; dyspnoea
	Cisapride	Increase acetylcholine (Ach) release	0.5 mg/kg orally q8h	Diarrhoea; abdominal pain
Decrease detrusor hyperreflexia	Propantheline bromide	Anticholinergic, antispasmodic	5–30 mg q8h 0.25–0.5 mg/kg orally q8h	Pupillary dilation; decrease GI motility; constipation; dry mucous membranes
	Oxbutynin chloride	Direct antispasmodic	2-5mg q8h-q12h	Urine retention; vomiting; constipation; tachycardia
Increase urethral tone	Phenylpropanolamine	α-adrenergic agonist	5-50 mg orally q8h 1.5 mg/kg orally q8h-q12h	CNS stimulation; tachycardia; urine retention
	Imipramine	α- and β-adrenergic stimulation	5–15 mg orally q12h	Seizures; tremors; hyperexcitability
	Diethylstilbestrol	Increase sphincter sensitivity to norepinephrine (noradrenaline)	0.1–1.0 mg orally for 3–5 days then 1.0 mg weekly	Bone marrow suppression; oestrus
	Testosterone	Unknown	2.2 mg/kg i.m. q30days	Prostatic hypertrophy; behaviour changes

Medical management of micturition disorders. <sup>a</sup> Dose for dogs unless otherwise stated. CNS = central nervous system; GI = gastrointestinal. (continues)

Desired effect	Drug	Mechanism of action	Dosage <sup>a</sup>	Side-effects
Decrease urethral tone	Phenoxybenzamine	α-adrenergic antagonist	0.25–0.5 mg/kg orally q12h–q24h	Hypotension; tachycardia
ofonulavo cu guro raymian piecovini sol fonulari z	Prazosin	α-adrenergic antagonist	Dogs: 1 mg/15 kg orally q12h–q24h Cats: 0.25–0.5 mg orally q12h–q24h	Hypotension; tachycardia
	Diazepam	Skeletal muscle relaxant	Dog: 2-10 mg q6h-q8h Cat: 1-2.5 mg q8h	Hepatotoxicity in cats; sedation; excitement
	Dantrolene	Skeletal muscle relaxant	Dog: 1–5 mg orally q8h–q12h Cat: 0.5–2 mg/kg orally q8h	Weakness; GI upset; sedation; hepatotoxicity

18.22

(continued) Medical management of micturition disorders. a Dose for dogs unless otherwise stated. CNS = central nervous system; GI = gastrointestinal.

continuous urinary catheterization techniques. Manual expression is indicated if the bladder is easily expressed but residual urine should be periodically monitored by ultrasonography or urinary catheterization. Large residual volumes will predispose to UTIs. Urine culture should be periodically performed.

# **Prognosis**

The prognosis depends on the underlying disorders of micturition. If the underlying disorder is reversible and properly diagnosed, the prognosis is generally good. Chronic disorders with associated micturition dysfunction have a less favourable or more guarded prognosis. Some disorders may require life-long monitoring and medical management. UTIs pose the most serious complication of micturition dysfunction.

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# **Neurological emergencies**

# Simon R. Platt and Natasha J. Olby

# Introduction

Neurological emergencies require rapid and accurate decision making and treatment. Inappropriate management in the early stages of disease can have catastrophic consequences for the animal. Studies on acute head injury (Brain Trauma Foundation, 2000) and on status epilepticus in humans, show that having an emergency protocol in place improves the outcome. Thus, to ensure optimal treatment in an emergency situation, it is recommended that emergency protocols that take into account the availability of staff and equipment for each clinic are developed pre-emptively. The aims of this chapter are firstly to describe the aetiology and pathophysiology of common neurological emergencies, including acute spinal cord injury, head trauma and status epilepticus, and secondly to use this information to develop guidelines for assessing and managing each problem.

# **Acute spinal cord injury**

Acute onset of non-ambulatory para-, hemi- or tetraparesis should be considered an emergency.

## Aetiology

The most common causes of acute spinal cord injury include type I intervertebral disc herniation, vertebral fractures and luxations, vascular disease (e.g. fibrocartilaginous embolism (FCE) and haemorrhage), cervical stenotic myelopathy (Wobbler syndrome) and congenital malformation causing instability (e.g. atlantoaxial subluxation) (Figure 19.1). Many chronic diseases, such as neoplasia, discospondylitis and inflammatory or infectious spinal cord diseases, can also present acutely as a result of the sudden development of associated pathology (i.e. vertebral fractures due to vertebral neoplasia or discospondylitis, intraparenchymal haemorrhage due to haemangiosarcoma and vasculitis). These diseases are described in Chapters 13–15.

# **Pathophysiology**

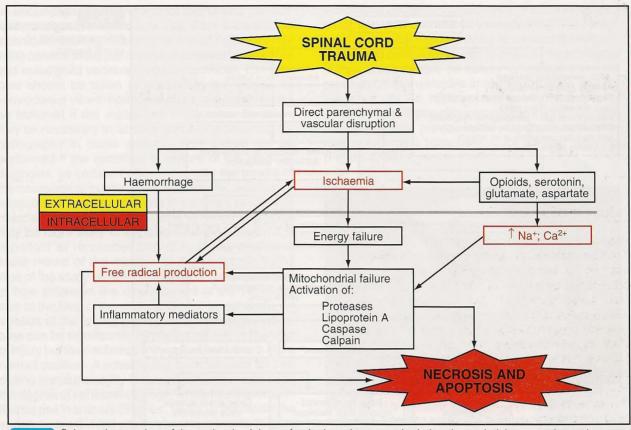
Acute onset of spinal cord dysfunction is most commonly caused by a combination of one or more events including concussion, compression, ischaemia, or laceration of the spinal cord.

2	
Disease	Type of spinal cord injury
IVDD [14, 15]	Concussion and compression
Vertebral fracture/ luxation [14,15,19,21]	Concussion, compression, laceration. Ongoing instability
FCE [14,15]	Ischaemia
Haemorrhage [14,15]	Ischaemia and compression
Congenital instability (e.g. AA subluxation) [14]	Concussion, compression $\pm$ laceration. Ongoing instability
Neoplasia [13-15]	Compression ± vertebral fracture
Discospondylitis [13–15]	Compression, inflammation, ± vertebral fracture. Ongoing instability
Myelitis [10, 15]	Inflammation

Type of spinal cord injury associated with different diseases. The most common causes of acute paresis are in bold type. Square brackets indicate chapters detailing the respective diseases. FCE = fibrocartilaginous embolism; IVDD = intervertebral disc disease.

# Concussion

Concussion of the spinal cord is commonly caused by intervertebral disc extrusion, as well as vertebral fractures and luxations. Repeated concussion may occur in some diseases due to vertebral instability. Acute concussion of the spinal cord initiates a series of biochemical and metabolic events that expand the primary zone of tissue necrosis. The majority of this secondary damage occurs within 24 hours of injury and, although cellular apoptosis continues for weeks to months (Crowe et al., 1997), it is not common for clinical signs of deterioration to be evident much beyond 72 hours after the injury. The detrimental events are initiated by the initial mechanical insult, which causes release of neurotransmitters, damage to glial and neuronal cell membranes and damage to local vasculature. This causes energy failure and increased cell membrane permeability, and leads to a cascade of events, including destruction of the microvascular bed, leading to a progressive reduction in perfusion of the injured area, an increase in intracellular calcium concentrations, and free-radical production. Many of these factors interact to produce a cycle of destructive events. The end result is an expanding zone of cellular necrosis and apoptosis (Figure 19.2) (Olby, 1999; Dumont et al., 2001).



Schematic overview of the pathophysiology of spinal cord trauma, depicting the underlying vascular and biochemical components of secondary injury.

#### Ischaemia

19.2

Primary ischaemic injuries (e.g. FCE) initiate a similar biochemical and metabolic cascade but the injury is centred on the zone of the embolized blood vessel, often producing very asymmetrical and focal signs (see Chapters 14 and 15).

# Compression

Compression of the spinal cord is commonly due to intervertebral disc protrusion, extramedullary and intradural neoplasia, and malalignment of the vertebral canal. Compression interferes directly with axonal ion channel function, myelin sheath integrity (Shi and Blight, 1996) and vascular perfusion of the affected area (Griffiths *et al.*, 1978; Milhorat *et al.*, 1996) causing demyelination and eventually axonal, glial and neuronal necrosis.

# Laceration

Laceration of the spinal cord by external objects (e.g. gunshot wounds) or internally (luxation of the vertebrae) not only interrupts blood supply and concusses and compresses the spinal cord, but also causes axonal transection. As central nervous system (CNS) axons do not regenerate effectively, the consequences of this are extremely serious.

## Assessment of the spinal injury patient

An approach to the assessment and management of spinal injury is presented in Figure 19.3.

#### Primary assessment

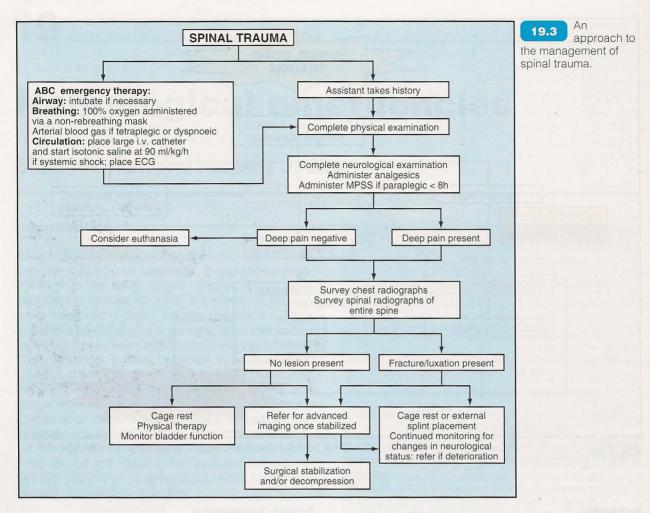
On admission, the first aim is to stabilize the patient by assessing the airway, breathing and circulation ('ABC') and treating abnormalities where necessary as for any other emergency. Complete routine blood work and urinalysis should be obtained if possible; otherwise a packed cell volume (PCV), total protein level, blood urea nitrogen (BUN) assessment and glucose and electrolyte levels should be ascertained. Cardiovascular stability should be investigated with the aid of an electrocardiogram (ECG) and blood pressure measurements. The important systemic parameters to monitor, their suggested reference values after trauma and management protocols are similar to those following head trauma and are detailed later (see Figure 19.13).

## Secondary assessment

A thorough physical and orthopaedic examination can follow the initial patient evaluation and stabilization. Consideration should also be given to obtaining a coagulation panel, a buccal mucosal bleeding time and a platelet count if there has been associated haemorrhage. A patient that has experienced blood loss, or that is expected to do so during surgery, should be blood-typed or cross-matched and appropriate blood products should be obtained.

#### Neurological assessment

The neurological examination should be aimed at localizing the lesion and determining its severity (see Chap-



ters 2, 14 and 15). Thoracolumbar spinal cord injury severity is commonly graded as follows (Griffiths, 1982):

- 0 Normal
- 1 Painful
- 2 Conscious proprioceptive deficits, ataxia and paraparesis
- 3 Paraplegia
- 4 Paraplegia with urinary incontinence and overflow
- 5 Paraplegia with loss of deep pain perception.

In tetraplegic animals, special attention should be paid to the respiratory rate and pattern with a view to detecting hypoventilation.

# **Diagnostic imaging**

Survey radiography: Thoracic radiographs should be evaluated after a significant trauma, looking for pleural effusions, contusions, pneumomediastinum and pneumothorax as well as the possibility of pericardial effusion and diaphragmatic herniation. If a vertebral injury is suspected, it is recommended that survey lateral radiographs are taken of the entire spine prior to additional manipulation of the animal. Sites particularly predisposed to fracture and luxation include the atlantoaxial junction, the thoracolumbar junction and the lumbar and lumbosacral spine. As some fractures can be subtle, good quality and well positioned radiographs from two different planes are necessary (Figure 19.4). This may





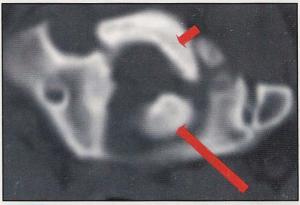
Radiographs of the cranial cervical spine of a 2year-old German Shepherd Dog following a traumatic accident. The lateral radiograph shows a comminuted fracture of C2 (arrowed), accompanied by evident dorsal subluxation of this vertebra with respect to C1. The ventrodorsal radiograph shows lateral displacement of C2 vertebra (arrowed) with respect to C1.

be accomplished with the animal awake and immobilized; analgesia may be required. Poor radiographic technique resulting in rotation of the spine (especially in the cervical area) can make assessment for unstable and malaligned vertebral segments difficult. Extreme care should be taken in positioning the animal for ventrodorsal views: horizontal beam radiographs can be obtained if the equipment is available. Sedation may be necessary to achieve accurate positioning for radiography in some animals. This should not be performed if the examiner is unsure of the physical diagnosis, as sedation often influences the results of the neurological examination. Additionally, sedation or anaesthesia results in the loss of voluntary paraspinal muscle contraction, and unstable vertebral segments may be more likely to subluxate (Bagley, 2000). It is important to remember that radiographs provide a static record of the location of the vertebrae at the time of the study but they do not allow for assessment of how extensive the displacement of the vertebrae was at the time of the injury and prior to radiology. As a result of the strong paraspinal musculature, vertebrae can be significantly displaced acutely at the time of injury but then subsequently pulled back into a more normal position. A scheme has been devised for predicting spinal instability in human patients based upon the degree of vertebral damage, which has been modified for use in animals (Shores, 1992). In this model the vertebrae are divided into three compartments (Figure 19.5). Damage to more than one compartment indicates a need for internal or external stabilization (see Chapter 15).

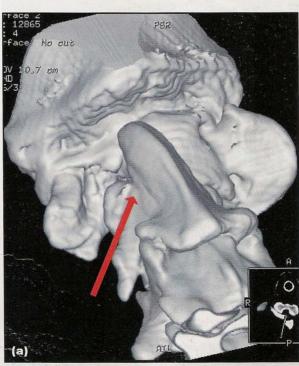
Dorsal Middle
Ventral

The three-compartment theory of assessment of 19.5 spinal trauma. The dorsal compartment contains the spinous processes and supporting ligamentous structures, in addition to the articular facets, laminae and pedicles. The dorsal longitudinal ligament, the dorsal vertebral body and the dorsal annulus of the disc are contained within the middle compartment. The ventral compartment contains the rest of the vertebral body, the lateral and ventral aspects of the annulus of the disc, the nucleus pulposus and the ventral longitudinal ligament. If two or more compartments are damaged, the fracture is considered unstable, whereas damage to just one compartment may indicate a stable fracture. This does not take into account associated compression of the spinal cord which may occur with damage to just one of these compartments.

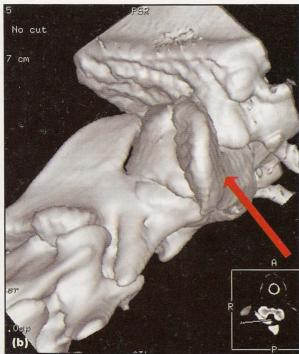
Advanced imaging: Myelography or other advanced imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) is needed to evaluate spinal cord compression and to ensure that additional lesions unidentifiable on survey radiographs are not present. CT is invaluable in identifying bone defects that may not be apparent on survey radiography (Figure 19.6). Three-dimensional reconstruction from CT images may provide additional anatomical information regarding bone contour for surgical planning (Figure 19.7).



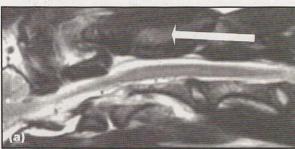
Transverse bone window CT scan of C1 and C2 of a 16-month-old German Shepherd Dog with neck pain, following a possible traumatic incident. The dens (longer arrow) can be seen within the vertebral canal but is displaced laterally. The dorsal lamina of C1 (short arrow) can be identified and is mis-shapen as a result of a congenital malformation (see Figure 19.7). (Courtesy of Fraser McConnell)

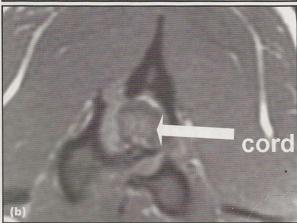


3-D CT reconstruction of the case described in 19.6. (a) Dorsal oblique view: the arrow indicates C2. C1 is malformed with partial absence of the right neural arch and mis-shapen wing. (Courtesy of Fraser McConnell) Figure 19.7b overleaf.



19.7b 3-D CT reconstruction of the case described in 19.6. (b) Ventrolateral view: the arrow indicates the ventral surface of C1, which is fused to the occipital bone. (Courtesy of Fraser McConnell)





MR images of the German Shepherd Dog in Figure 19.4. (a) Sagittal T2-weighted MR image of the cervical vertebrae and spinal cord. Although the degree of bone definition is not as good as that seen with CT examination, the effect of injury – such as compression on the spinal cord and its parenchyma – can be assessed accurately in three views. The arrow indicates the dorsal arch of C2. (b) Transverse T2-weighted MR image of C2. Note that there is no evident compression of the cord, despite the comminuted nature of the fracture of the vertebra itself.

MRI has the distinct advantage of showing intramedullary spinal cord structure and soft tissue injuries as well as multiplanar images but may not provide enough bone detail when compared with CT studies (Figure 19.8).

# Urinary tract assessment

In addition to blood urea and creatinine values and urine specific gravity levels, urethral catheterization may be required in patients that have undergone a severe concurrent abdominal or pelvic trauma in order that urine production may be assessed over the next 72 hours. This will also be of value in those patients with systemic shock due to the traumatic event. Abdominal ultrasonography may be required to evaluate the bladder wall and kidneys, and to detect the presence of free abdominal fluid; contrast-enhanced imaging of the urinary tract may provide further information on the function and form of the individual structures.

# **Prognosis**

Factors influencing the prognosis of the acutely paralysed animal include the nature of the underlying disease, the severity of the neurological signs and the duration of the signs.

# Severity of neurological signs

Deep pain perception in affected limbs is the single most important prognostic indicator of injury severity that can be obtained from the neurological examination (Figure 19.9).

Disease	Prognosis for recovery	
Acute intervertebral disc herniation	50–75% chance of recovery with surgery within 24 hours (Anderson <i>et al.</i> , 1991; Duval <i>et al.</i> , 1996; Scott and McKee 1999; Olby <i>et al.</i> , 2003)	
Spinal fracture/ luxation	< 5% with displaced vertebrae < 25% if no displacement (Olby et al., 2003)	
FCE	No information available. If no recovery of deep pain after 2 weeks, prognosis is guarded	
Haemorrhage (bleeding disorder or rodenticide)	Guarded	
Neoplasia	Guarded	

19.9 Prognosis of paraplegic animals with loss of pelvic limb deep pain perception as a result of different diseases.

Deep pain sensation is tested for by applying heavy pressure to the bones of the digits with large haemostatic forceps or heavy pliers such that pressure is applied to the underlying periosteum. Deep pain is present if the animal displays a conscious awareness of the stimulus rather than simply a reflex withdrawal of the limb (Chapter 1). Typically, both medial and lateral digits of each paralysed limb are tested and the tail is tested. Lack of deep pain perception implies *functional* spinal cord or peripheral nerve transection at the time of testing and provides useful prognostic information. As a general rule, animals with intact deep pain perception have the potential to recover motor function if the underlying disease process can be prevented from progressing.

The prognosis for paraplegic animals that lack deep pain perception in their pelvic limbs varies with the cause (see Figure 19.9) and is generally worse with longer duration of the signs. It is unusual to be presented with a tetraplegic animal that lacks deep pain perception as functional cervical spinal cord transection causes paralysis of the respiratory muscles. In addition, the sympathetic nervous system is interrupted as it runs down the cervical spinal cord, resulting in pronounced bradycardia. As a result, animals with extremely severe cervical spinal cord injuries die rapidly of hypoventilation and cardiac arrest.

# Guidelines for the treatment of spinal cord injury

Spinal fractures and luxations are considered in more detail in Chapter 15.

#### **Medical treatment**

Medical treatment of acute spinal cord concussion and ischaemia is aimed at limiting the final extent of secondary tissue damage.

Minimizing secondary injury is generally achieved by ensuring adequate perfusion and oxygenation of the animal and administration of neuroprotective agents. Treatment must be initiated as soon as possible after injury, as the majority of secondary tissue damage occurs within 24 hours of the primary injury.

Stabilization: The first consideration is systemic blood pressure and oxygenation, particularly in the trauma victim. In the normal spinal cord, perfusion is maintained in the face of changes in systemic blood pressure by an autoregulatory process. Autoregulation is lost in the injured spinal cord, and hypotension results in a further decrease in the already compromised perfusion of the injured segment. Hypoxaemia exacerbates the local energy failure. Hypotension should be treated by administration of appropriate fluids (see Head trauma section) and oxygen supplementation provided by face mask or nasopharyngeal or transtracheal catheter if necessary.

**Neuroprotection:** Unfortunately there is little (if any) objective information available on the most effective treatment for acute spinal cord injury in dogs, and so treatment protocols for humans with acute spinal cord injuries have been adopted by veterinary surgeons. It should be emphasized that the efficacy of these protocols has not been established in dogs with spontaneous spinal cord injuries.

Although many different therapeutic agents, including opioid antagonists and agonists, calcium channel blockers and glutamate receptor antagonists, have been shown to be protective experimentally (for a more complete review see Olby, 1999), the only drugs shown to be of benefit in randomized prospective clinical trials are methylprednisolone sodium succinate (MPSS) and its derivative, tirilizad (Bracken *et al.*, 1985, 1997; Bracken and Holford, 1993).

MPSS remains the standard of care in humans (Bracken, 2002). MPSS has been shown to be effective because of its free radical scavenging properties rather than its anti-inflammatory effect (Hall et al., 1995). In order to obtain this effect, it must be used at high doses and treatment should be initiated within 8 hours of injury. Suggested protocols are detailed in Figure 19.10. Delaying initiation of treatment for more than 8 hours has a detrimental effect on outcome in people (Bracken and Holford, 1993). As MPSS has both glucocorticoid and free-radical scavenging effects, it is postulated that delaying treatment until after the majority of free-radical-induced damage has occurred is more likely to result in glucocorticoid-induced side-effects. Indeed, although there continues to be widespread use of glucocorticoids such as dexamethasone to treat acute spinal cord injuries in veterinary practice, there is no good evidence that such drugs are beneficial and the side-effects have been well documented (Toombs et al., 1980). Contraindications to the use of high-dose MPSS are:

- The presence of voluntary motor function, as such animals have an excellent prognosis for return of function without MPSS
- Recent treatment with corticosteroids or nonsteroidal anti-inflammatory agents in view of the risk of GI complications
- An interval of > 8 hours elapsed since loss of ambulation.

Time elapsed since injury	Suggested MPSS protocol		
< 3 hours	30 mg/kg i.v. injection followed by 5.4 mg/kg/ hour CRI for 24 hours OR followed by 15 mg/kg i.v. injections at 2 and 6 hours after the initial injection then 2.5 mg/kg CRI for 18 hours		
3–8 hours	30 mg/kg i.v. injection followed by 5.4 mg/kg/ hour CRI for 48 hours OR followed by 15 mg/kg i.v. injections at 2 and 6 hours after the initial injection then 2.5 mg/kg CRI for 42 hours		
> 8 hours	MPSS contraindicated		

Suggested protocols for MPSS administration in patients with acute spinal cord injuries taken from human clinical trials (Bracken *et al.*, 1997). CRI = continuous rate infusion.

Non-surgical treatment of spinal fractures and luxations is dependent on whether the injury is determined to be unstable based on the three-compartment model shown in Figure 19.5. If there is no instability, cage rest for 6 weeks is adequate (Carberry et al., 1989). If the fracture/luxation is determined to be unstable and owners decline surgery, an external splint can be placed in such a manner that the damaged area of the spine is immobilized (for further details, see Chapters 14 and 15; see also Patterson and Smith (1992) and Selcer et al. (1991)). If the animal has significant skin, abdominal or thoracic injuries, splint placement may be contraindicated, in which case the animal should be strictly cage rested for 6 weeks.

# Surgical treatment

Animals with compressive lesions or spinal instability should ideally undergo surgical decompression and stabilization as soon as possible.

The surgical treatment of intervertebral disc disease (IVDD) is addressed in Chapters 15 and 21, that of Wobbler syndrome and atlantoaxial subluxation in Chapters 14 and 21 and that of spinal fractures and luxations in Chapters 14, 15 and 21.

# **Head trauma**

Severe head trauma is associated with high mortality in human beings and animals. Although there is no standard of care for head trauma in human medicine, a series of guidelines have been developed centred around maintaining adequate cerebral perfusion (Brain Trauma Foundation, 2000). The appropriate therapy for head trauma patients remains controversial in veterinary medicine due to a lack of objective information on the treatment of dogs and cats with head injuries.

Treatment of affected animals must be immediate to increase the chance of recovery to a level that is both functional, and acceptable to the owner.

Many dogs and cats can recover from severe brain injuries if systemic and neurological abnormalities that can be treated are identified early enough.

# Aetiology

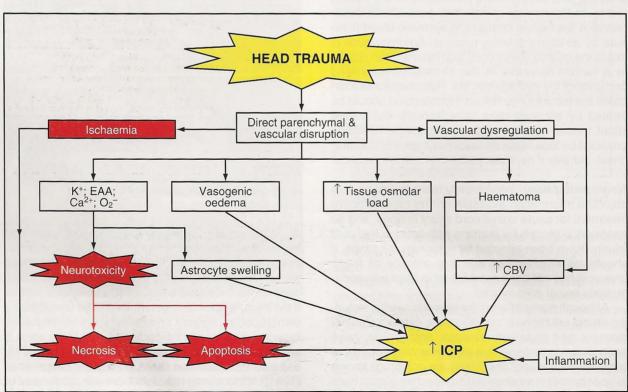
Common causes of head injuries in cats and dogs include road traffic accidents, falls, kicks, gunshot or pellet wounds and bites from larger animals. Traumatic injuries to the brain may result from blunt or penetrating insults.

# Pathophysiology

The underlying vascular and cellular pathophysiology of head trauma is similar to that described for spinal cord trauma, but is complicated by elevations in intracranial pressure (ICP) (Figure 19.11). ICP has enormous importance because of its effect on cerebral perfusion. Cerebral perfusion pressure is equal to systemic blood pressure minus the ICP and so elevations in ICP result in decreased perfusion of the brain (see Chapter 20). Increases in ICP are therefore often responsible for clinical decline after head trauma.

After head trauma, the volume of the brain tissue compartment increases usually due to oedema or haemorrhage (Bagley, 1996). As the brain tissue compartment increases, the cerebrospinal fluid (CSF) and the blood compartments must decrease or intracranial pressure will increase (see Chapter 20).

Compensation for increased brain tissue volume initially involves the translocation of CSF out of the skull; this is followed by decreased production of CSF and, eventually, decreased cerebral blood flow (Dewey, 2000). These compensatory mechanisms prevent increases in ICP for an undetermined period. Once the ability for compensation is exhausted, a further small increase in intracranial volume will result in dramatic



Schematic overview of the pathophysiology of head trauma as it relates to the increase of intracranial pressure (ICP), depicting the underlying vascular and biochemical components of secondary injury. CBV = cerebral blood volume; EAA = excitatory amino acids.

elevations of ICP, with the immediate onset of clinical signs (see Chapter 20).

The clinical manifestations of ICP elevations include anisocoria, miosis, mydriasis, altered mentation and loss of motor function (see below).

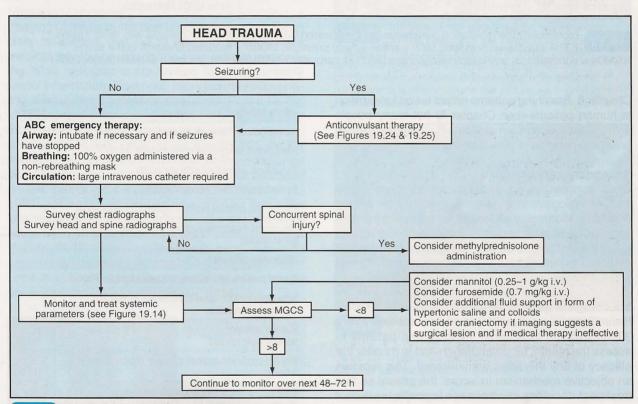
# Assessment of the head trauma patient

# Primary assessment

As with all types of acute injury, the 'ABC' (airway, breathing, cardiovascular status) of emergency care is extremely important (Figure 19.12).

Initial physical assessment of the severely braininjured patient focuses on imminently life-threatening abnormalities. The major parameters that need to be assessed initially and continuously are listed in Figure 19.13. It is important not to focus first on the patient's neurological status, as many patients will be in a state of hypovolaemic shock following a head injury, which can exacerbate a depressed mentation. Hypovolaemia and hypoxaemia need to be recognized and addressed immediately. In addition, a minimum essential database includes a PCV, total protein level, a blood urea level, glucose and electrolyte levels as well as a urine specific gravity.

Respiratory system dysfunction can be common after head injury. The most dramatic respiratory abnormality seen following head injury can be neurogenic pulmonary oedema (NPO). Neurogenic pulmonary oedema is usually self-limiting if the patient survives, and will resolve in a matter of hours to days, but can cause severe dyspnoea, tachypnoea and hypoxaemia. Hypoxaemia exacerbates the development of secondary tissue damage. The patterns of ventilation seen with cerebral diseases such as head trauma are described in



19.12 An approach to management of head trauma. MGCS = modified Glasgow coma score.

Monitoring parameters	Suggested goal .	Suggested treatment
Neurological examination	MGCS >15	Ensure head elevation (30 degrees) Ensure all points below are addressed Consider mannitol (see text) Consider surgery (see text)
Blood pressure	MAP 80–120 mmHg	Adjust fluid therapy Pressor support (dopamine 2–10 μg/kg)
Blood gases	$P_aO_2 \ge 80 \text{ mmHg}$ $P_aCO_2 < 35-40 \text{ mmHg}$	Oxygen supplementation Consider mechanical ventilation

The monitoring parameters and suggested goals of treatment for patients with head trauma. ICP = intracranial pressure; MAP = mean arterial pressure; MGCS = modified Glasgow coma score; NSAIDs = non-steroidal anti-inflammatory drugs (such as carprofen). (Modified from Johnson and Murtaugh, 2000) (continues)

Monitoring parameters	Suggested goal	Suggested treatment
Pulse oximetry (SPO <sub>2</sub> )	<i>SP</i> O <sub>2</sub> ≥ 95%	Oxygen supplementation Consider mechanical ventilation
Heart rate and rhythm	Avoid tachy- and bradycardias Avoid arrhythmias	Adjust fluid therapy Treat for pain Express bladder frequently Address ICP Treat arrhythmias specifically
Central venous pressure	5–12 cm H <sub>2</sub> O	Adjust fluid therapy
Respiratory rate and rhythm	10–25/min	Ventilate if necessary
Body temperature	37–38.5°C	Passive warming or cooling NSAIDs if pyrexic
Electrolytes	(See laboratory normal values)	Adjust fluid therapy; supplement fluids accordingly
Blood glucose	4–6 mmol/l	Adjust fluid therapy Consider dextrose administration
Intracranial pressure	5–12 mmHg	As for MGCS abnormalities

(continued) The monitoring parameters and suggested goals of treatment for patients with head trauma. ICP = intracranial pressure; MAP = mean arterial pressure; MGCS = modified Glasgow coma score; NSAIDs = non-steroidal anti-inflammatory drugs (such as carprofen). (Modified from Johnson and Murtaugh, 2000)

Chapter 8. Breathing patterns reflect lesion localization in human patients (see Chapter 8) but many people believe there is no clinical localizing value to specific breathing patterns in veterinary patients.

#### Secondary assessment

Once normovolaemia and appropriate oxygenation and ventilation are established (see below), the patient should be thoroughly assessed for traumatic injuries. These include skull, vertebral and long-bone fractures as well as splenic torsions and ruptured bladder and ureters. The neurological examination, cranial imaging and ICP measurement can then be considered.

# Neurological assessment

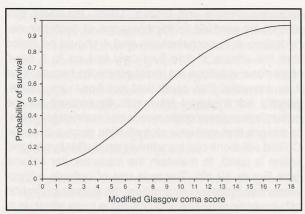
Neurological assessment should be repeated every 30-60 minutes in severely head-injured patients to assess the patient for deterioration and to monitor the efficacy of any therapies administered. This requires an objective mechanism to 'score' the patient so that treatment decisions can be made logically.

The modified Glasgow coma scoring system: In humans, traumatic brain injury is graded as mild, moderate or severe on the basis of an objective scoring system, the Glasgow coma scale (GCS). A modification of the GCS has been proposed for use in veterinary medicine (Shores, 1989) (Figure 19.14). The scoring system enables grading of the initial neurological status and serial monitoring of the patient. Such a system can facilitate assessment of prognosis, which is crucial information for both the veterinary surgeon and owner (Platt et al., 2001) (Figure 19.15).

The modified scoring system incorporates three categories of the examination (level of consciousness; motor activity; brainstem reflexes) which are assigned a score from 1 to 6, providing a total score of 3 to 18, with the best prognosis being the higher score.

Motor activity	Score
Normal gait, normal spinal reflexes	6
Hemiparesis, tetraparesis or decerebrate rigidity	5
Recumbent, intermittent extensor rigidity	4
Recumbent, constant extensor rigidity	3
Recumbent, constant extensor rigidity with opisthotonus	2
Recumbent, hypotonia of muscles, depressed or absent spinal reflexes	1
Brainstem reflexes	
Normal pupillary light reflexes and oculocephalic reflexes	6
Slow pupillary light reflexes and normal to reduced oculocephalic reflexes	5
Bilateral unresponsive miosis with normal to reduced oculocephalic reflexes	4
Pinpoint pupils with reduced to absent oculocephalic reflexes	3
Unilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	2
Bilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	1
Level of consciousness	
Occasional periods of alertness and responsive to environment	6
Depression or delirium, capable of responding but response may be inappropriate	5
Semi-comatose, responsive to visual stimuli	4
Semi-comatose, responsive to auditory stimuli	3
Semi-comatose, responsive only to repeated noxious stimuli	2
Comatose, unresponsive to repeated noxious stimuli	1

19.14 Modified Glasgow coma scale.



Probability of survival of the head trauma patient during the first 48 hours after admission, expressed as a function of the modified Glasgow coma score. (Reproduced from Platt et al., 2001, J. Vet. Internal Medicine, with permission)

# Diagnostic imaging

Imaging of the patient's head is often indicated, especially in animals that fail to respond to aggressive medical therapy or deteriorate after initially responding. Skull radiographs are unlikely to reveal clinically useful information about brain injury but may occasionally reveal evidence of calvarial fractures (Figure 19.16).

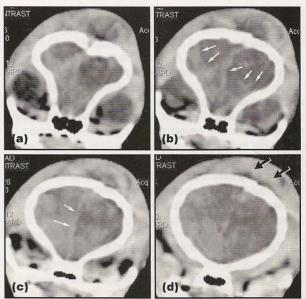
Computed tomography is the preferred modality for imaging the head in cases of severe head injury. Even patients with 'mild' head trauma can exhibit abnormalities on the CT scan and so the initial decision to image the patient's head should not be based on the neurological examination alone (Platt *et al.*, 2002). CT image acquisition time is faster and often less expensive than MRI and CT also demonstrates acute haemorrhage and bone detail better than MRI (Figure 19.17). However, MRI has been shown to provide key information relevant to the prognosis based upon its ability to detect subtle parenchymal damage not evident on CT imaging (Figure 19.18).



# 19.16

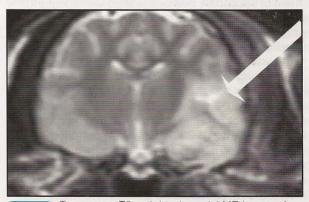
Dorsoventral skull radiograph of a 6-year-old Hungarian Vizla following an incident causing head trauma. Note the large linear calvarial fracture (arrowed). Such images do not provide any useful information about associated parenchymal damage or haematomas. (Courtesy of Jacques Penderis)

Cervical spinal radiographs are also advised at the time of any skull imaging to rule out concurrent spinal lesions (Olby *et al.*, 2001). As for spinal trauma (see above), thoracic radiographs will help to evaluate for evidence of thoracic and cardiac trauma.



The skull of this dog was crushed by a bite.

(a) The fracture of the frontal bone is clearly visible. (b) The arrows point out the border between oedematous and more normal tissue. (c) Arrows demonstrate the midline shift resulting from oedema. (d) Oedema is also visible in the soft tisues overlying the skull (arrowed).



Transverse T2-weighted cranial MR image of a 1-year-old Domestic Shorthair cat that was hit by a car. It is difficult to appreciate the damage to the calvarium on MRI but the associated parenchymal damage can be identified (arrowed).

# Intracranial pressure monitoring

Medical and surgical decisions based on ICP measurements rather than on gross neurological findings have decreased morbidity and mortality in human head trauma victims. ICP monitoring is a standard procedure for human head trauma management but has only recently been investigated in dogs and cats. Unfortunately, the extremely high cost of the fibre-optic system needed is likely to limit its use in veterinary medicine, but other systems may become available to enable ICP monitoring to be an integral part of head trauma management in dogs and cats. For example, transcranial Doppler ultrasonography can be used to measure the resistive index of blood flow in the basilar artery. This has been shown to be an indirect measure of intracranial pressure in dogs (Fukushima et al., 2000) and to correlate with the severity of neurological signs in hydrocephalic dogs (Saito et al., 2003).

#### Urinary tract assessment

Urinary output should be monitored and if it is elevated (> 2–3 ml/kg/h) for at least 2 consecutive hours, central diabetes insipidus (DI) should be considered, which may result from severe damage to the hypothalamic area. Diagnosis is based upon the presence of high serum sodium as well as low urine sodium and low urine osmolality. Polyuria due to fluid overload, hyperglycaemia and therapeutic osmotic diuresis must be ruled out in the diagnosis of central DI. Oliguria (in the absence of hypovolaemia) may indicate the syndrome of inappropriate antidiuretic hormone secretion, if it is accompanied by hyponatraemia and increased urine sodium; however, hypotension, pain and even stress can cause a similar situation.

#### Guidelines for treatment of head trauma

The most important consideration in head injury is maintenance of cerebral perfusion by treatment of hypotension and elevated ICP.

Considerations for management of head trauma have been outlined in Figure 19.13. As well as ensuring adequate cerebral perfusion, head injury management is aimed at measures to prevent and limit the development of secondary nervous system damage, as in the case of spinal cord trauma (see above).

# **Medical therapy**

Minimizing increases in ICP: Simple precautions can be taken in positioning the animal, with its head elevated at a 30-degree angle from the horizontal to maximize arterial supply to, and venous drainage from, the brain (Dewey, 2000). It is also important to ensure that there is no constrictive collar obstructing the jugular veins, as this would immediately elevate ICP.

Fluid therapy: The basic goal of fluid management of head trauma cases is to maintain a normovolaemic to slightly hypervolaemic state. There is no support for attempting to dehydrate the patient in an attempt to reduce cerebral oedema and this is now recognized to be deleterious to cerebral metabolism. In contrast, immediate restoration of blood volume is imperative to ensure normotension and adequate CPP (see Chapter 20).

Initial resuscitation usually involves intravenous administration of hypertonic saline and/or synthetic colloids (Figure 19.19). Use of these solutions allows rapid restoration of blood volume and pressure while limiting the volume of fluid administered. In contrast, crystalloids will extravasate into the interstitium within an hour of administration and thus larger volumes are required for restoration of blood volume. As a result this could lead to exacerbation of oedema in head trauma patients.

Hypertonic saline administration (4–5 ml/kg over 5–10 minutes) draws fluid from the interstitial and intracellular spaces into the intravascular space, which improves blood pressure and cerebral blood pressure and flow, with a subsequent decrease in intracranial

pressure (Proulx and Dhupa, 1998). However, this should be avoided in the presence of systemic dehydration or hypernatraemia and it should be noted that the effects of this fluid only last up to 1 hour. Hypertonic solutions act to dehydrate the tissues; thus it is essential that crystalloid solutions are subsequently administered (at a rate to account for the patient's maintenance demands and insensible losses) to ensure that systemic dehydration does not occur. Colloid solutions can be administered after hypertonic saline is used, to maintain the intravascular volume (see Figure 19.19). The sole use of colloids will not prevent dehydration; in addition, the co-administration of hypertonic solutions and colloids is more effective at restoring blood volume than either alone.

Fluid	Half-life (hours)	Average molecular weight (Daltons)	Dose	
Oxypolygelatin	2.5	30,000	Maximum daily dose	
Succinylated gelatin	2-4	35,000	20 ml/kg Rates: Dog: up to 10–20	
Pentastarch	2.5	280,000	ml/kg/hour	
Hetastarch	25	450,000	Cat: up to 5-10 ml/kg/hour (preferably	
Dextran 40	2.5	40,000	with CVP monitoring to ensure volume overloa	
Dextran 70	25	70,000	does not occur)	

Colloid type, characteristics and dose for use in the head trauma patient.

Osmotic diuretics: Osmotic diuretics such as mannitol are very useful in the treatment of intracranial hypertension. Mannitol has an immediate plasma-expanding effect that reduces blood viscosity and increases cerebral blood flow and oxygen delivery. This results in vasoconstriction within a few minutes, causing an almost immediate decrease in ICP. The better known osmotic effect of mannitol reverses the blood—brain osmotic gradient, thereby reducing extracellular fluid volume in both normal and damaged brain.

Mannitol should be administered as a bolus over a 15-minute period, rather than as an infusion, in order to obtain the plasma-expanding effect; its effect on decreasing brain oedema takes approximately 15-30 minutes to establish and lasts between 2 and 5 hours (Dewey, 2000). Doses of 0.25-1 g/kg appear to be equally effective in lowering ICP, but the duration of effect is shorter with the lower doses. Repeated administration of mannitol can cause an accompanying diuresis, which may result in volume contraction, intracellular dehydration and the concomitant risk of hypotension and ischaemia. It is therefore recommended that mannitol is reserved for the critical patient (Glasgow coma score < 8) or the deteriorating patient. There has been no clinical evidence to prove the theory that mannitol is contraindicated in the presence of intracranial haemorrhage. There is evidence that the combination of mannitol with furosemide (0.7 mg/kg) may lower ICP in a synergistic fashion, especially if furosemide is given first (Bagley et al., 1996).

**Arterial blood pressure support:** Presence of arterial hypotension despite fluid resuscitation (see above) may require administration of vasoactive agents such as dopamine (2–10 μg/kg/min). Conversely, arterial hypertensive episodes ('Cushing's response') may be managed with calcium channel blockers such as amlodipine (0.625–1.25 mg/cat q24h; 0.5–1.0 mg/kg in dogs q24h). However, the authors recommend treating the increased ICP aggressively before using drugs to assist blood pressure regulation.

**Oxygenation and ventilation:** Hyperoxygenation is recommended for most acutely brain-injured animals. Partial pressure of oxygen in the arterial blood ( $P_aO_2$ ) should be maintained as close to normal as possible (at or above 80 mmHg).

Supplemental oxygen should be administered initially via face mask, as oxygen cages are usually ineffective because constant monitoring of the patient does not allow for a closed system. As soon as possible, nasal oxygen catheters or transtracheal oxygen catheters should be used to supply a 40% inspired oxygen concentration with flow rates of 100 ml/kg/min and 50 ml/kg/min, respectively. If the patient is in a coma, immediate intubation and ventilation may be needed if this is indicated by blood gas evaluations. A tracheostomy tube may be warranted in some patients for assisted ventilation (Dewey, 2000).

Hyperventilation has traditionally been known as a means of lowering abnormally high ICP through a hypocapnic cerebral vasoconstrictive effect. However, hyperventilation is a 'double-edged sword'. Besides reducing the ICP, it induces potentially detrimental reductions in the cerebral circulations if the  $P_{\rm a}{\rm CO_2}$  level is < 30–35 mmHg. The major difficulty with hyperventilation is the inability to monitor the presence and effects of ischaemia on the brain. It is important that animals do not hypoventilate, and such animals should be ventilated to maintain a  $P_{\rm a}{\rm CO_2}$  of 30–40 mmHg. Aggressive hyperventilation can be used for short periods in deteriorating or critical animals.

Seizure prophylaxis: Although the role of prophylactic anticonvulsants in preventing post-traumatic epileptic disorders remains unclear, seizure activity greatly exacerbates intracranial hypertension in the head injury patient. For this reason, it is recommended that all seizure activity in these patients should be treated aggressively. As most cases need to be treated parenterally, phenobarbital (2 mg/kg i.m. or i.v. q6–8h) is recommended. This can be continued for 3–6 months (2–4 mg/kg p.o. q12h) after the trauma and can then be slowly tapered off if there have been no further seizures. Phenobarbital will have the additional benefit of reducing cerebral metabolic demands and therefore acts as a cerebral protectant but the clinician should be cautious of the sedative side-effects.

Corticosteroids: Corticosteroids have been studied extensively in head injury. Clinical human trials have not shown a beneficial effect of corticosteroids, including MPSS, in the treatment of head injury. In addition, they have been associated with increased

risks of infection, are immunosuppressive, cause hyperglycaemia leading to cerebral acidosis, and have other significant effects on metabolism. Their use is not recommended.

Nutritional support: Nutritional support is essential in the management of the head injured patient. Such support has been shown to improve the neurological recovery as well as shorten the time to recovery. On a short-term basis, a nasogastric tube can be used to deliver peptide-rich compounds; caution should be used when placing and maintaining these tubes as they may cause sneezing, which may elevate intracranial pressure. For medium- to long-term management, pharyngostomy or oesophagostomy tubes should be used (see Chapter 20). If there is brain stem damage, a gastrostomy tube should be inserted, in case of poor oesophageal function. Care should be taken to avoid hyperglycaemia, which may promote cerebral acidosis in brain-damaged individuals (Johnson and Murtaugh, 2000). For details on the above procedures and on diet selection, the reader is directed to more comprehensive descriptions (Marks, 1998).

#### Surgical therapy

A description of the surgical techniques for intracranial surgery can be found elsewhere. Although it is rare that surgery is indicated in head injury cases, there are several specific abnormalities that can be associated with an episode of head trauma that may warrant the consideration of surgical treatment, as follows.

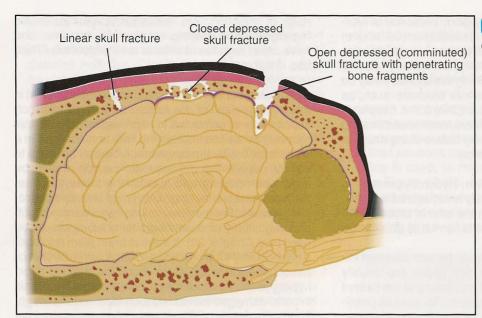
Acute extra-axial haematomas: Generous craniotomies are generally indicated once these abnormalities have been diagnosed with imaging (Dewey et al., 1993). If the haematoma is due to a fracture across a venous sinus, there may be profuse bleeding associated with surgical intervention. The need for blood transfusions should be expected. Haematoma removal also risks the chance of bleeding from previously compressed vessels.

**Calvarial fractures:** A skull fracture per se may or may not have significant implications for patient management. Skull fractures are typically differentiated based upon:

- Pattern (depressed, comminuted, linear) (Figure 19.20)
- Location
- Type (open, closed).

A fracture is generally classed as depressed if the inner table of the bone is driven in, to a depth equivalent to the width of the skull. All but the most contaminated, comminuted and cosmetically deforming depressed fractures can be managed without operative intervention.

Acute intraparenchymal haematoma: In contrast to acute extra-axial haematomas, acute intraparenchymal clots may be managed conservatively, unless subacute enlargement of initially small intraparenchymal clots is identified with repeat imaging.



Schematic illustration of three categories of skull fracture.

Haemorrhagic parenchymal contusions: Most haemorrhagic contusions do not require surgical management. The main indication for surgery with these types of lesions is limited to cerebellar contusions with compression of the 4th ventricle and brainstem; surgery aims to reduce the potential for further compression and herniation, which can develop over the initial 24–48 hours.

Intracranial hypertension (ICH): Benefit can be found when decompressive procedures (craniectomy and durectomy) are carried out before irreversible bilateral pupillary dilation has developed (Bagley, 1996). However, 'prophylactic' decompressive surgery seems inappropriate before non-surgical management of elevated ICH has been carefully maximized.

# Status epilepticus and cluster seizures

Status epilepticus (SE) can be defined as continuous seizure activity lasting for 30 minutes or longer, or repeated seizures with failure to return to normality within 30 minutes (Engel, 1989). Cluster seizures describe the occurrence of multiple seizure events within a 24-hour period.

SE and severe cluster seizures can cause permanent neurological sequelae or even death. Immediate treatment is necessary. There is some evidence to suggest that early aggressive treatment of prolonged seizures results in their termination with smaller doses of medication and less overall risk to the patient than would be incurred by delaying therapy. In addition, profound haemodynamic and metabolic abnormalities commonly occur during seizures and may cause significant morbidity despite appropriate treatment of the seizures. Management of SE requires a prompt, comprehensive and dynamic approach and should be individualized, depending on the animal's clinical status (Boothe, 1998) (Figure 19.21).

# Aetiology of SE and cluster seizures

Causes of status epilepticus are listed in Figure 19.22.

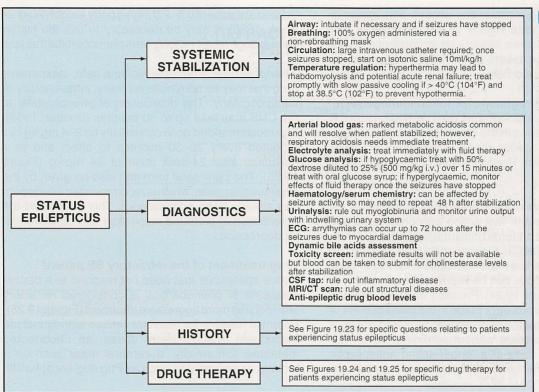
Risk factors for SE and cluster seizures in veterinary patients are not well documented; however, body weight has been established as the only significantly different variable between dogs that have SE and those that do not (Saito *et al.*, 2001).

Studies evaluating SE and cluster seizures in dogs admitted to veterinary hospital have not revealed a specific cause for the seizures in 25–28% of the cases (Bateman and Parent, 1999; Platt and Haag, 2002). Approximately 28% of the cases are diagnosed with primary (genetic or idiopathic) epilepsy. Secondary epilepsy (dogs with an identifiable structural cause within the brain; Podell *et al.* (1995)) is the cause of the seizures in 32-35% of the cases, whilst reactive epileptic seizures (RES) are seen in 7–12% of the cases. However, RES have been reported as being responsible for up to 50% of SE cases in one study (Gandini *et al.*, 2003).

Chronic processes that cause SE include preexisting epilepsy in which SE is caused by breakthrough seizures or the discontinuation of antiepileptic drugs. CSF abnormalities have been documented in up to 73.5% of dogs with either SE or cluster seizures. Results of neuroimaging (MRI or CT) can be abnormal in up to 46% of SE cases (Platt and Haag, 2002).

# **Pathophysiology**

During the early stages of SE, the seizures can be accompanied by increased autonomic discharge, the systemic manifestations of which include tachycardia, hypertension and hyperglycaemia. After about 30 minutes, physiological deterioration can ensue with the patient developing hypotension, hypoglycaemia, hyperthermia and hypoxia (Russo, 1981). Incessant skeletal muscle contractions and impaired ventilation may lead to lactic acidosis, hyperkalaemia, hypoxia, hypercarbia and hyperthermia. Severe myoglobinuria, resulting from hyperthermia-induced rhabdomyolysis, may additionally cause impairment of renal function, especially when accompanied by systemic hypotension.



#### 19.21

Approach to systemic stabilization and management of the status epilepticus patient.

Class of epilepsy	Mechanisms of disease	Specific diseases
Primary	Idiopathic	Breed-related Familial
Secondary	Degenerative	Storage diseases
	Anomalous	Hydrocephalus
	Neoplasia (primary or metastatic)	Meningioma Glial cell tumour Choroid plexus papilloma Lymphoma
	Inflammatory: infectious	Viral Rickettsial Bacterial Fungal Parasitic
	Inflammatory: sterile	Granulomatous meningoencephalitis Breed-specific encephalitides
	Trauma	Acute Chronic
	Vascular	Infarction Haemorrhage
Reactive seizures	Metabolic	Hepatic encephalopathy Hypoglycaemia Hypocalcaemia Electrolyte imbalances
	Toxic	Organophosphate Lead Metaldehyde
Other	Low anticonvulsant concen	rations

9.22 Classification and causes of status epilepticus.

# **Management of SE**

Guidelines to management of status epilepticus are outlined in Figure 19.21. A team approach to patients in SE will be beneficial in accomplishing emergency stabilization, therapeutic intervention and diagnostic investigation simultaneously. Although immediate anticonvulsant therapy and systemic stabilization are warranted (see below), concurrent history taking (Figure 19.23), physical examination and diagnostic tests may be useful at the same time.

- 1. When did the episode start?
- 2. Is there a pre-existing seizure disorder?
- 3. Has the patient had status epilepticus or cluster seizure events before?
- 4. Have there been any systemic health problems within the last 4 months?
- 5. Has there been any change in the patient's personality or behaviour within the last 4 months?
- 6. Is the patient on medications including anticonvulsant therapy?
- 7. Which anticonvulsants are being given; what is the dose; when was the last dose?
- 8. How long has the patient been on anticonvulsants?
- 9. Have any recent serum anticonvulsant levels been performed?
- 10. Is there any recent trauma, travel history or toxin exposure?
- 11. Has the patient eaten a meal within the last few hours?

19.23 Important questions to ask about the patient in status epilepticus.

#### Systemic stabilization of the SE patient

The initial care of a patient with SE involves basic medical emergency measures, namely the ABC of life support, but also includes oxygenation, attention to electrolyte, glucose, BUN levels and acid-base

status, obtaining intravenous access and temperature regulation (see Figure 19.13). In patients with pre-existing seizures already on antiepileptic drugs, blood should be taken at the initial evaluation for drug level measurement.

Drug treatment regimens for initial management

Due to the relative lack of objective information to guide veterinary surgeons in the choice of the optimal treatment regimen, a wide range of treatment practices has been adopted. Recommendations are outlined in Figure 19.24.

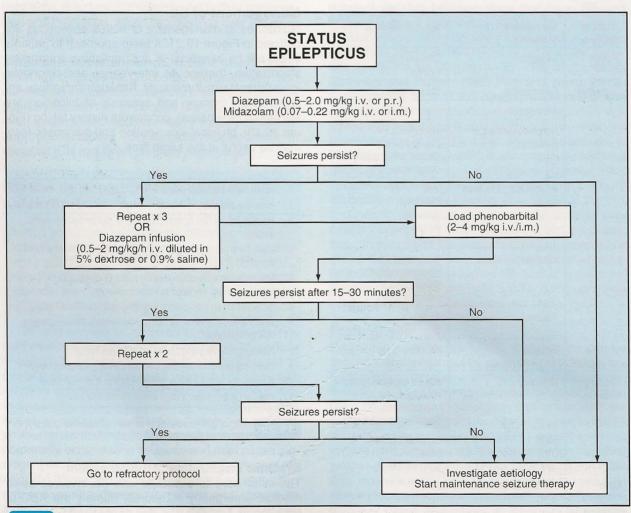
Benzodiazepines: Benzodiazepines, such as diazepam, are potent, fast-acting anticonvulsants and therefore are the preferred initial therapy in SE (Boothe, 1998). Braund (2003) recommended the use of 0.5–2.0 mg/kg i.v., up to a maximum dose of 20 mg, in dogs and cats. This dose can be repeated to effect two or three times (Figure 19.24). Probably the most common and most dangerous error made in the management of SE is to treat repeated seizures with repeated doses of intravenous diazepam without administering an adequate loading dose of a longer-acting antiepileptic drug. Rectal administration of diazepam may be con-

sidered at a dose of 0.5–2.0 mg/kg body weight (Wagner *et al.*, 1998). It may be necessary to use the higher dose in dogs receiving long-term phenobarbital therapy.

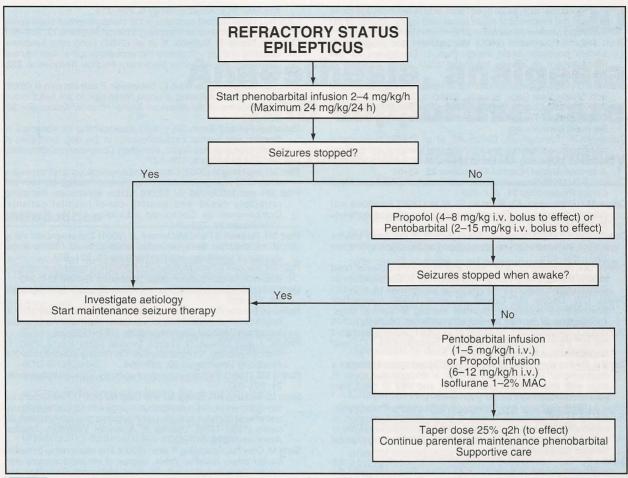
*Phenobarbital:* Phenobarbital is a safe, inexpensive drug that may be administered orally, intravenously or intramuscularly. The distribution of phenobarbital to the CNS may take up to 30 minutes (Boothe, 1998). The recommended dose can initially be 2–4 mg/kg i.v., repeated every 20–30 minutes to effect and to a maximum total 24-hour dose of 24 mg/kg (Figure 19.25). The parenteral form can also be given by the intramuscular route, which is recommended if diazepam has already been administered. This may avoid the potentiation of profound respiratory and cardiovascular depression.

#### Drug treatment of the refractory SE patient

Status epilepticus that does not respond to a benzodiazepine or phenobarbital is considered refractory and requires more aggressive treatment (Figure 19.25). Potential reasons for resistant seizure activity include inadequate anticonvulsant doses, an uncorrected metabolic abnormality, a cerebral mass such as a tumour, or encephalitis such as Pug dog encephalitis.



19.24 Approach to the initial pharmacological management of the status epilepticus patient.



Approach to the pharmacological management of the refractory status epilepticus patient. MAC = minimum 19.25 alveolar concentration.

**Propofol:** Propofol has barbiturate- and benzodiazepine-like effects and can suppress CNS metabolic activity. Propofol can be administered by intravenous bolus (4-8 mg/kg, to effect) or by constant-rate infusion (0.1-0.6 mg/kg/min or 6-12 mg/kg/h) (Heldmann et al., 1999). However, this drug should be used with caution, preferably in settings where definitive airway control and haemodynamic support are possible, as hypoxaemia secondary to apneoa is a primary side effect, as is myocardial depression.

Barbiturates: Thiopental and pentobarbital have potential, though unproven, cerebral protective effects in the management of SE. These drugs will almost always control the physical manifestations of seizures but with negligible anticonvulsant properties. Pentobarbital should be given to effect rather than at a specific dose (2-15 mg/kg i.v.), as there is tremendous individual variation in response (Figure 19.25) (Indrieri, 1989).

Inhalational anaesthetics: These are recommended only as a last resort in cases of resistant SE (Platt and McDonnell, 2000). Isoflurane, an inhalational general anaesthetic agent, may be efficacious in the treatment of resistant SE but may need to be used for an extensive period of time. Obviously, isoflurane therapy necessitates ventilation and intensive-care monitoring, and hypotension may occur during therapy.

Potassium bromide: A small study on the use of loading doses of potassium bromide administered intrarectally (100 mg/kg q4h for 24 hours) indicated that this drug is both well absorbed and safe when used in this manner (Dewey et al., 1999). The clinical effect of this regimen has yet to be evaluated.

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# Anaesthesia, analgesia and supportive care

Anthea L. Raisis and Jacqueline C. Brearley

# Introduction

To select an appropriate sedative or anaesthetic technique for animals with neurological disease, a basic understanding of physiology and pathophysiology of the disease is essential. Discussed in this chapter are:

- The physiological and pathophysiological aspects of neurological disease relevant to anaesthesia and analgesia
- The information used to develop a rational approach to anaesthetizing the neurological patient
- The supportive care required by animals undergoing anaesthesia and analgesia.

# **Intracranial pressure**

The aim of anaesthesia in animals with central nervous system (CNS) disease is preservation of neuronal function. Normal neuronal function depends on adequate cerebral blood flow.

#### Factors that influence cerebral blood flow

Cerebral blood flow (CBF) is equal to cerebral perfusion pressure (CPP) divided by cerebral vascular resistance (CVR), where CPP is mean arterial blood pressure (MABP) minus intracranial pressure (ICP). Thus:

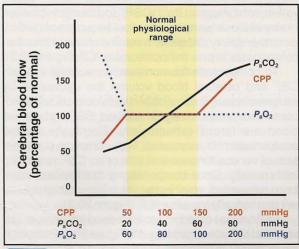
CBF = (MABP - ICP)/CVR

# Regulation of cerebral vascular resistance

Cerebral blood flow is regulated by local mechanisms that alter cerebral vascular resistance, including autoregulation, flow metabolism coupling and chemical regulation.

 Autoregulation is a myogenic reflex that maintains constant blood flow by altering vascular resistance in response to changes in transmural pressure. In normal brain tissue, autoregulation operates at CPPs between 50 and 150 mmHg, provided that fluctuations within this range are not rapid. Outside this normal physiological range, CBF changes linearly with MABP (Figure 20.1).

- Flow-metabolism coupling describes the linear relationship between CBF and cerebral metabolic rate. Increases in cerebral metabolic rate result in increased consumption of glucose and oxygen and increased production of local tissue metabolites such as H+ ions, adenosine and potassium, which dilate cerebral arterioles and thus increase cerebral blood flow (CBF). Conversely, decreases in cerebral metabolic rate result in decreased CBF and cerebral blood volume (CBV), due to arteriolar constriction.
- Chemical regulation of CVR is influenced by many factors. Of relevance to the anaesthetist are the effects of arterial carbon dioxide and oxygen. Carbon dioxide (CO<sub>2</sub>) is a potent arterial vasodilator in the CNS. Outside the normal physiological range, increases in the partial pressure of arterial CO<sub>2</sub> (P<sub>a</sub>CO<sub>2</sub>) cause decreased CVR and increased CBF. Conversely, decreases in PaCO2 promote cerebral vasoconstriction, increased CVR and associated decreases in CBF (Figure 20.1). Partial pressure of arterial oxygen (PaO2) also influences CBF: outside the normal physiological range, decreases in P<sub>a</sub>O<sub>2</sub> cause arterial vasodilation and thus increases in CBF (Figure 20.1).



Relationship between cerebral blood flow and cerebral perfusion pressure (CPP), arterial  $CO_2$  tension ( $P_2CO_2$ ) and arterial  $O_2$  tension ( $P_2O_2$ ).

In normal brain tissue these mechanisms ensure that cerebral blood flow is maintained within adequate levels for normal neuronal function. However, these mechanisms can be altered by disease and by administration of pharmacological agents, with serious consequences.

# Factors that influence mean arterial blood pressure

An in-depth discussion of cardiovascular physiology is beyond the scope of this chapter but can be found in Levick (1999).

- Systemic arterial blood pressure (SABP) is dependent on cardiac output and systemic vascular resistance (SVR).
- Cardiac output is determined by the product of stroke volume (SV) and heart rate (HR).
- Stroke volume is influenced by preload, cardiac contractility and afterload.
- Preload is influenced by venous return, which is influenced by relative or absolute circulating blood volume.
- Afterload is predominantly influenced by vascular tone and peripheral vascular resistance.

Alterations in any of the factors that influence cardiac output or SVR by disease or pharmacological agents can alter MABP and subsequently alter CPP and CBF.

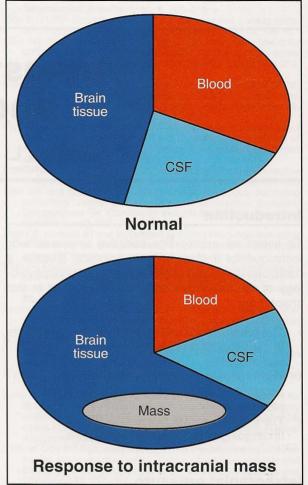
# Factors that influence intracranial pressure

Increased ICP occurs when pathological increases in intracranial tissue volume exceed compensatory decreases in other intracranial tissues. The result is decreased CPP, which causes neuronal ischaemia, dysfunction and, ultimately, neuronal death (Bagley, 1996).

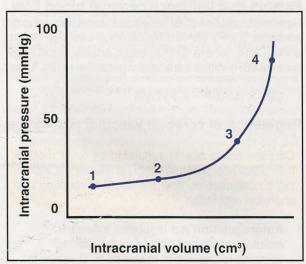
The CNS is surrounded by rigid bony structures. As a result, the volume of the intracranial contents is fixed. Intracranial contents consist of solid tissue, tissue water, cerebrospinal fluid (CSF) and blood. Increases in any of these components must be accompanied by a compensatory decrease in volume of one of the other components to prevent increases in ICP (Figure 20.2).

To compensate for increased intracranial volume, CSF and cerebral blood volume are decreased by increased tissue absorption and translocation, and vaso-constriction, respectively. In addition, CSF and venous blood are forced extracranially. Eventually volume compensation is exhausted, with complete compression of venous sinuses and little or no CSF remaining intracranially. Once compensatory mechanisms have been exhausted, small increases in intracranial volume will dramatically increase ICP (Figure 20.3).

Factors that contribute to increased intracranial volume and ICP are summarized in Figure 20.4. Pathological increases in intracranial volume and ICP can be due to increased soft tissue (tumour, abscess, haematoma), increased tissue water (oedema) or increased CSF



The total volume of intracranial contents (brain tissue, blood, cerebrospinal fluid) is fixed. Thus, an increase in one component is accompanied by a compensatory decrease in one or both of the others. An increase in ICP occurs if the compensatory mechanisms are exceeded.



Relationship between intracranial pressure (ICP) and volume. Between points 1 and 2 compensatory mechanisms exist, and increases in intracranial volume produce minimal changes in ICP. However, once the compensatory mechanisms have been exhausted, small increases in intracranial volume will dramatically increase ICP (points 3 and 4).

Mechanism	Cause	Management
Pathological	Mass (tumour, abscess) Tissue fluid (oedema, inflammation) Haemorrhage/haematoma Hydrocephalus	Mannitol: 0.25–1.0 g/kg i.v. Furosemide 0.7 mg/kg i.v. Corticosteroids for neoplasia: Methylprednisolone 10–30 mg/kg i.v. Dexamethasone 0.2–0.5 mg/kg i.v. Craniectomy and durotomy
Physiological	Increased venous blood volume: Jugular vein obstruction Head-down position Increased intrathoracic pressure (as a result of IPPV) Increased CVP; fluid overload  Increased arterial blood volume: Increased ABP Increased P <sub>a</sub> CO <sub>2</sub> Decreased P <sub>a</sub> O <sub>2</sub> Increased cerebral metabolic rate: seizures, pyrexia, drugs	Decrease venous blood volume: Careful patient positioning Head elevation (< 30 degrees) Monitor CVP during IPPV and intravenous fluid therapy  Increased arterial blood volume: Maintain normotension Ventilate to normocapnia Supplement oxygen Decrease cerebral metabolic rate: treat seizures, eliminate pyrexia, choose appropriate drugs
Pharmacological	Direct arterial or venous dilation Interference with autoregulation, chemical responsiveness and flow-metabolism coupling	Select anaesthetic agents that decrease cerebral metabolic rate (thus reducing cerebral blood flow) to counteract effect of vessel dilation Select agents that minimally alter autoregulation, flowmetabolism coupling and chemical responsiveness

20.4

Summary of causes and treatment of increased intracranial pressure. ABP = arterial blood pressure; CVP = central venous pressure; IPPV = intermittent positive pressure ventilation.

volume (hydrocephalus). Physiological increases in intracranial volume and ICP are associated with increased cerebral blood volume, which may be venous or arterial.

- Increased cerebral venous blood volume can be due to physiological or pharmacological venodilation or interference with venous flow.
   Causes of decreased venous flow include: obstruction of jugular veins; ventroflexion of the neck; increased intrathoracic pressure during intermittent positive pressure ventilation (IPPV); and increased central venous pressure (CVP), which could be due to excessive intravenous fluid administration or cardiac failure.
- Increased cerebral arterial blood volume is caused by physiological factors or pharmacological intervention causing arterial vasodilation. Decreases or increases in MABP and associated CPP stimulate an autoregulatory response that causes reflex arterial vasodilation or constriction in an attempt to maintain CBF. In contrast, when brain autoregulation is diminished (brain disease, inhalation agents), CBF and CBV increase linearly with MABP. Thus high MABP (hypertension) causes increased CBF and associated increases in CBV and ICP, and hypotension results in decreased CBF. Cerebral vasodilation and associated increases in CBF, CBV and ICP are also caused by increased cerebral metabolic rate, increased  $P_a$ CO<sub>2</sub> and decreased  $P_a$ O<sub>2</sub>.

Anaesthetic agents alter CBV and ICP by directly affecting the cerebral vasculature or by altering cerebral autoregulation, flow-metabolism coupling and chemical responsiveness.

# Stabilization of increased ICP

Any patient with increased ICP, regardless of cause, requires stabilization before anaesthesia or sedation for further work-up is considered. Osmotic diuretics such as mannitol are very effective in reducing ICP and are usually the first-line treatment for stabilizing patients with increased ICP. Administration of corticosteroids is found to be beneficial in vasogenic cerebral oedema, such as is associated with neoplasia, but has not been observed to reduce ICP in other disease states. In an emergency, intubation and cautious hyperventilation may be warranted (see Chapter 19).

# **Diuretics**

Mannitol is administered at 0.25–1.0 g/kg i.v. over 10–15 minutes. Although an almost immediate effect is seen, peak effect occurs within 60 minutes of administration. Repeated dosing every 4 hours can be used if necessary but ultimately causes dehydration, hypotension and ischaemia.

Mannitol decreases ICP partly by increasing the osmotic gradient between intravascular and extravascular fluid compartments, causing fluid to move out of tissues into the blood. The increase in blood volume decreases ICP due to the dilutional effects on packed cell volume (PCV) and the resultant decrease in blood viscosity. Decreased blood viscosity improves oxygen delivery, which ultimately stimulates cerebral vasoconstriction and decreased cerebral blood volume (Bagley, 1996). The osmotic effects of mannitol on ICP are effective for 16–48 hours, after which brain tissue accommodates to the new osmolality. Fluid restriction after mannitol therapy has been associated with poor

outcome in human patients (Clifton *et al.*, 2002), thus it is imperative that intravenous fluid therapy is instigated to ensure that patients remain normovolaemic.

Furosemide is a loop diuretic that inhibits the sodium/potassium/chloride ion pump in the thick ascending loop of Henlé, resulting in decreased sodium and water reabsorption. Concurrent administration of furosemide at 0.7 mg/kg i.v. has been reported to be synergistic with mannitol for reducing ICP (Bagley, 1996). Adverse effects of loop diuretics include hypokalaemia and dehydration; thus fluid and electrolyte balance needs to be monitored closely if these agents are used.

# Hyperventilation

Hyperventilation to achieve a  $P_{\rm a}{\rm CO_2}$  of 30 mmHg can be used for stabilization of acute, transient increases in ICP, particularly when herniation is imminent (Barbaccia and Williams, 2001).

Hyperventilation decreases ICP by causing respiratory alkalosis and stimulates constriction of cerebral arterioles. Prolonged hyperventilation is not recommended, as associated vasoconstriction may worsen neuronal injury by decreasing oxygen supply to normal areas of the brain (Kiening *et al.*, 1997; Barbaccia and Williams, 2001). It is therefore recommended that

 $P_{\rm a}{\rm CO_2}$  should not decrease below 30 mmHg, thus minimizing ischaemia in normal regions of the brain. The degree of ventilation should be monitored using capnography or, ideally, direct blood gas analysis. It is important to remember that damaged areas of brain lose the ability to autoregulate and do not reliably constrict. When hyperventilation is used to assist with stabilization of the patient with increased ICP, it must be used carefully with close monitoring of the patient.

# Haemodynamic stabilization

Adequate cerebral perfusion requires a CPP of 50–60 mmHg. In the absence of ICP monitoring, it is recommended that MABP be maintained between 80 and 100 mmHg, in order to 'achieve' this CPP (Cornick, 1992).

Cerebral perfusion pressure is determined by the difference between MABP and ICP. Thus, maintenance of cerebral perfusion in patients with increased ICP requires maintenance of adequate MABP. Therapy used to improve MABP, such as intravenous fluid therapy, should be guided by CVP to prevent excessive increases in CVP, which will decrease CSF drainage and exacerbate increases in ICP. Characteristics of fluids that can be used are summarized in Figure 20.5.

Category	Type of fluid	Osmolality (mOsm/l)	Uses	Comments
Hypotonic crystalloids	5% glucose	252	Hypoglycaemia: 2 ml/kg/h	Blood glucose elevation exacerbates neuronal injury in ischaemic tissues; thus, glucose-containing fluids should be avoided in intracranial and spinal cord disease
	Lactated Ringer's/ Hartmann's solution	250–260	Rehydration: 2 ml/kg/h + % dehydration + losses Intraoperative: 10 ml/kg/h	Can increase brain water content, especially if administered in large amounts
Isotonic crystalloids	Polyionic isotonic crystalloid (e.g. Plasmalyte)	312	Rehydration: 2 ml/kg/h + % dehydration + losses Intraoperative: 10 ml/kg/h	Preferred rehydration solution for CNS disease
	0.9% saline	308	Rehydration: 2 ml/kg/h + % dehydration + losses Intraoperative: 10 ml/kg/h	Prolonged use causes hyperchloraemic metabolic acidosis
Isotonic colloids	Etherified starch 6% (e.g. Hetastarch)	310	Rapid expansion of blood volume: up to 20 ml/kg/h	Maximum dose 20 ml/kg/day to prevent side-effects associated with bleeding Small dogs/cats (<5 kg) at greater risk of fluid overload
	Haemoglobin glutamer-200 (bovine)	Not reported	Resuscitation (when blood unavailable): up to 10 ml/kg/h	Nitric oxide scavenger: may have detrimental effect on cerebral autoregulation and CBF. Use cautiously in neurological patient Small dogs/cats (<5 kg) at greater risk of fluid overload
Hypertonic crystalloids	7.2% saline	2400	Resuscitation: Dogs: 4–5 ml/kg over 5–10 min Cats: 2 ml/kg over 5–10 min	Can decrease brain water content Useful for resuscitation in head trauma Must be used with isotonic crystalloid to prevent tissue dehydration

Summary of crystalloid and colloid fluid characteristics and suitability for use in animals with central nervous system disease. CBV = cerebral blood flow.

20.5

Colloids and hypertonic saline solutions allow more rapid restoration of circulating blood volume and subsequent normotension, using smaller volumes of fluid than crystalloids. Administration of hypertonic solutions causes plasma volume expansion by osmotic movement of intracellular and interstitial fluid into the intravascular space. This effect may have the added benefit of reducing brain water content and ICP. It is important to remember that cellular and systemic dehydration and electrolyte abnormalities will occur following administration of hypertonic saline unless follow-up administration of isotonic crystalloids or even colloids is performed. Fluid therapy for animals with intracranial disease is discussed in more detail below and in Chapter 19. For more details on the use of hypertonic saline, see Dibartola (2000).

## Positioning

Careful positioning of the patient to prevent occlusion of jugular veins and achieve mild head elevation is recommended for animals with increased ICP.

It is important to remember that excessive head elevation will decrease blood pressure within the cerebral cavity, due to the hydrostatic effects of gravity, and thus will decrease CPP. It is recommended that head elevation does not exceed 30 degrees.

#### **Intracranial disease**

# Anaesthesia

Considerations for anaesthetizing animals with intracranial disease are summarized in Figure 20.6. For more details, see Matta *et al.* (2000).

#### Sedation

Heavy sedation can be used in healthy animals to allow diagnostic tests such as radiography and ultrasonography to be performed. In animals with clinical signs of intracranial disease, heavy sedation is generally avoided as this may lead to hypoventilation and associated increases in ICP. In addition, heavy sedation will interfere with the accurate assessment of the neurological status of the animal and thus may delay the instigation of appropriate therapy. In these cases anaesthesia is preferable, as it allows the airway to be protected and ventilation to be controlled. In addition, many anaesthetic agents, such as propofol and barbiturates, have the added benefit of reducing the cerebral metabolic rate, which helps to reduce neurological injury in these animals.

#### Premedication

Premedication is generally limited to an analgesic agent unless the animal is particularly anxious. When anxiolysis is required, the choice of agents is somewhat controversial. Characteristics of agents used for sedation or premedication are listed in Figure 20.7.

Problem	Aetiology	Anaesthetic management	
Decreased CPP	Decreased MABP  Increased ICP	Maintain MABP at 80–100 mmHg Maintain normovolaemia Drugs that minimally depress cardiovascular function See Figure 20.4	
Haemodynamic instability Sympathetic stimulation: Stress, struggling Intubation and extubation Surgical stimulus		Reduce sympathetic stimulation: Excitement-free induction Minimize pressor response to intubation/extubation Provide analgesia	
Hypoventilation Brainstem disease or forebrain disease with compression of brainstem		Pre-oxygenate Monitor adequacy of ventilation Provide assisted/mechanical ventilation when necessary	
Seizure activity	Forebrain disease	Avoid agents that decrease seizure threshold or that are epileptogenic	
Aspiration pneumonia  Brainstem disease: cranial nerve deficits cause decreased laryngeal reflexes, dysphagia and megaoesophagus		Rapid intubation and control of airway Consider feeding by gastrostomy tube	
Fluid and electrolyte abnormalities	Dehydration: decreased food and water intake Diseases of pituitary/hypothalamus: Cushing's, diabetes insipidus, inappropriate salt wasting Polyuria associated with chronic corticosteroid administration increases risk of dehydration	Correct fluid and electrolyte imbalances prior to anaesthesia	
Alteration in drug pharmacokinetics Phenobarbital administration: Competes with protein-bound drugs Induces cytochrome P450 enzyme metabolism		Decrease dose of drugs that exhibit high protein binding Increase frequency of administration of drugs metabolized by cytochrome P450	
Alteration in drug CNS pathology Phenobarbital administration		Exacerbation of the CNS depressant effects of anaesthetic agents requires careful administration $\pm$ dose reduction	

Considerations for anaesthetizing animals with intracranial disease. CNS = central nervous system; CPP = cerebral perfusion pressure; ICP = intracranial pressure; MABP = mean arterial blood pressure.

Agent	CBF regulation	Direct CV effects	CMR	ICP	Seizure activity	Comments	Dose
Acepromazine maleate	NR	Arterial VD and hypotension	NR	NR	†ulususa sajaansa sessusas	Avoid in intracranial disease Useful anxiolytic Ensure normovolaemia	0.01–0.02 mg/kg i.m.
Alpha-2 agonists	Flow- metabolism coupling \$\mathbf{J}\$	Initial arterial VC with hypertension Arterial VD and hypotension	1	No effect	† alfah atan takumnus	Avoid in intracranial disease Useful in fractious animals Ensure normovolaemia	Medetomidine: Dogs: 2–10 μg/kg i.m. Cats: 5–20 μg/kg i.m.
Opioids	Normal	Bradycardia Hypotension with rapid bolus	1	1		Reduce dose of induction and maintenance agents  Drug action – reduces response to intubation and surgical stimulus	See Figure 20.10
Benzodiazepines	Normal	No direct vascular effects	1	1	11	Possible sedative/anxiolytic Reduce induction agent dose Drug action – potentiates respiratory depression of other agents	Diazepam 0.1–0.2 mg/kg i.v. Midazolam 0.10.2 mg/kg i.v./i.m.
Lidocaine	Normal	Myocardial depression Hypotension	1	1	Low dose ↓ High dose ↑	Drug action – reduces response to intubation and extubation	1 mg/kg i.v.
Thiopental	Normal	Myocardial depression Arterial VD Hypotension	11	11		Drug action – may cause excitement in unsedated animals Accumulates with repeated dosing	Induction: up to 10 mg/kg i.v.
Propofol	Normal	Myocardial depression Arterial VD Hypotension	11	11	1	Excitement-free induction Suitable for maintenance of anaesthesia in dogs with intracranial disease	Induction: up to 2–4 mg/kg i.v. Maintenance: 0.2–0.4 μg/kg/min
Ketamine	Normal	Arterial VC Tachycardia Hypertension	11	1	1	Avoid in intracranial disease Avoid in animal at risk of seizures (myelography)	1–2 mg/kg i.v.

Characteristics of intravenous sedatives and induction agents used in animals and recommendations for use in animals with central nervous system disease. Commonly used dose rates are also provided. CBF = cerebral blood flow; CMR = cerebral metabolic rate; CV = cardiovascular; ICP = intracranial pressure; NR = not reported; VC = vasoconstriction; VD = vasodilation.

- Acepromazine maleate (ACP) is an anxiolytic commonly used in healthy animals. As this agent is reported to decrease seizure threshold, it has been recommended that it should not be used in animals that are at risk of seizures (Court et al., 1990a).
- Benzodiazepines, such as diazepam or midazolam, may be useful as anxiolytics in patients with intracranial disease. However, it must be remembered that the effects of benzodiazepines in small animals can be unpredictable and that excitement, dysphoria and disinhibition can occur (Court et al., 1990a). Thus, the use of these agents in animals with CNS disease should be undertaken with caution.
- Alpha-2 agonists, such as medetomidine, can produce marked sedation and significant cardiopulmonary dysfunction even when administered at low doses (Pypendop and Verstegen, 1998) and are best avoided in animals with intracranial disease.
- Administration of phenobarbital at 2–3 mg/kg i.m. is a useful premedication in some anxious dogs, when administered in conjunction with methadone.

#### Induction

Anaesthesia is induced using intravenous agents (see Figure 20.7) in order to provide a smooth induction with minimal struggling and rapid control of the airway.

Propofol is the agent most frequently used in animals with intracranial disease. It can be administered slowly to effect in minimally sedated animals without excitement. An additional advantage of propofol is that a single induction dose is metabolized more rapidly than thiopental, resulting in a more complete recovery.

Pre-oxygenation for 5–10 minutes and delivery of oxygen during induction are recommended to prevent hypoxaemia. Manual ventilation with a close-fitting mask during induction and rapid intubation can help to prevent hypercapnia.

Intubation and extubation are potent stimulators of the sympathetic nervous system. Resultant increases in heart rate and blood pressure can have marked effects on ICP. Pressor response associated with intubation can be minimized by administration of potent opioids (e.g. fentanyl), lidocaine or short-acting beta blockers such as esmolol. Bolus administration of potent opioids such as fentanyl (2–5 μg/kg i.v.) can cause significant bradycardia, hypotension and associated decreases in cerebral perfusion and marked respiratory depression. Ventilation is mandatory as soon as intubation is achieved in order to prevent hypercapnia and associated increases in ICP. Lidocaine administered at 1 mg/kg i.v. immediately prior to the induction agent has been used to obtund pressor response to intubation in dogs (Raisis *et al.*, 2002) but the efficacy of this agent has not been fully ascertained. Cats have increased sensitivity to parenteral lidocaine and in this species topical application on the larvnx is preferred.

#### Maintenance

Inhalation agents are still commonly used for maintenance of anaesthesia in animals with intracranial disease. Total intravenous anaesthesia is the preferred method during intracranial surgery in dogs.

The detrimental effects of volatile agents (Figure 20.8) can be minimized by using concurrent administration of potent opioids to reduce the dose of volatile agent used. Ventilating these animals to normocapnia also reduces detrimental effects of inhalation agents.

Total intravenous anaesthesia consists of continuous-rate infusions of propofol and potent opioids such as alfentanil or remifentanil. It is currently the preferred method in human neurosurgery and has recently been reported in canine neurosurgical patients (Raisis *et al.*, 2002). Due to slower metabolism of propofol in cats, accumulation and prolonged recoveries are likely. As a

result, inhalation anaesthesia with isoflurane or sevoflurane is still the preferred technique for use in cats. A technique using a combination of sevoflurane and alfentanil has been described for craniectomies in cats (Leece *et al.*, 2003).

The rationale for use of total intravenous anaesthesia in dogs is based on the beneficial effects of propofol on cerebral perfusion (see Figure 20.7) and its pharmacokinetics, which allow propofol to be administered by continuous infusion without accumulation and prolonged recovery. Concurrent infusion of opioids such as alfentanil and remifentanil (see Figure 20.10) is used to decrease the dose of propofol and thus reduce the effects of propofol on systemic cardiovascular function. In addition, continuous infusions of opioids help to minimize sympathetic stimulation and haemodynamic responses to surgery, which can have detrimental effects on CBF and ICP.

# **Patient position**

Positioning of the patient during surgery is important. It is essential to ensure that jugular veins are not occluded. Head elevation is also recommended, to help decrease ICP.

#### Monitoring

#### Ventilation:

IPPV is essential during anaesthesia of animals with intracranial disease, to ensure normocapnia ( $P_a$ CO<sub>2</sub> at 35–45 mmHg).

Adequacy of ventilation can be assessed using capnography but blood gas analysis is preferred during neurosurgery (see below).

Agent	CBF regulation	Direct CV effects	CMR	ICP	Seizures	Comments
Enflurane	Autoregulation ↓ Flow-metabolism coupling ↓ Chemical regulation ↓	Cerebral vasodilation Systemic BP 11	↓ (low ET%) ↑ (high ET%)		Torres Van Hang	Avoid in neurological patients
Halothane	Autoregulation \$\frac{1}{4}\$ Flow-metabolism coupling \$\frac{1}{4}\$ Chemical regulation \$\frac{1}{4}\$	Cerebral vasodilation Systemic BP 11	1	111	1	Avoid in neurological patients
Isoflurane	Autoregulation ↓ Flow-metabolism coupling ↓ Chemical regulation: normal	Cerebral vasodilation Systemic BP 11 -	The state of the s	†		Useful in neurological patients IPPV required to decrease detrimental effects on CBF
Sevoflurane	Autoregulation ↓ Flow-metabolism coupling ↓ Chemical regulation: normal	Cerebral vasodilation Systemic BP 11	1	1	Ţ	Useful in neurological patients IPPV required to decrease detrimental effects on CBF
Nitrous oxide	Not reported	Potent cerebral vasodilator Minimal systemic effects	No effect	f (potentiates other volatile agents)	No effect	Avoid in patients with increased ICP

Characteristics of inhalation agents used in animals and recommendations for use in animals with central nervous system disease. BP = blood pressure; CBF = cerebral blood flow; CMR = cerebral metabolic rate; CV = cardiovascular; ET% = end tidal percentage; ICP = intracranial pressure; IPPV = intermittent positive pressure ventilation.

#### Cardiovascular function:

Monitoring arterial blood pressure is important in order to ensure that adequate MABP and CPP are maintained. Monitoring CVP is important in order to ensure that venous return is not impaired and that hydration is adequate.

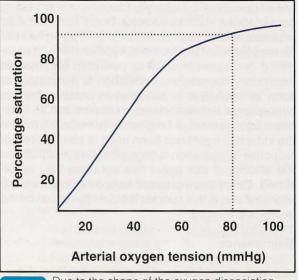
For intracranial surgical procedures, invasive monitoring of arterial blood pressure (ABP) and CVP is recommended. To ensure adequate CPP in patients with increased ICP, it is recommended that MABP is maintained between 80 and 100 mmHg. CVP in animals breathing spontaneously should normally be between 0 and 4 mmHg. IPPV will increase the mean CVP due to the increase in mean intrathoracic pressure. It is not unusual to observe CVP up to 8 mmHg in ventilated animals. High CVP (>10 mmHg) may indicate overhydration, decreased cardiac function or excessive pressures used for ventilation.

# Pulmonary function:

Monitoring pulmonary function is essential in order to ensure normocapnia ( $P_a\mathrm{CO}_2$  at 35–45 mmHg) and adequate oxygenation ( $P_a\mathrm{O}_2$  >80 mmHg). Capnography and pulse oximetry can be used as a guide to adequacy of pulmonary function. In critically ill animals or during intracranial surgery, direct measurement of arterial blood gases is recommended.

Capnography: This can be used to assess adequacy of ventilation. This technique measures  $\mathrm{CO}_2$  in the expired patient gases ( $P_{\mathrm{ET}}\mathrm{CO}_2$ ), which is equivalent to  $\mathrm{CO}_2$  tension in the alveoli ( $P_{\mathrm{a/v}}\mathrm{CO}_2$ ). As alveolar gases are in equilibrium with arterial blood,  $P_{\mathrm{ET}}\mathrm{CO}_2$  can be used to approximate  $P_{\mathrm{a}}\mathrm{CO}_2$ . In patients with cardiovascular (CV) compromise,  $P_{\mathrm{a}}\mathrm{CO}_2$  may differ from  $P_{\mathrm{ET}}\mathrm{CO}_2$  by as much as 10-20 mmHg, due to presence of physiological dead space. For short anaesthetic procedures, such as for diagnostic imaging or CSF sampling, capnography is adequate for monitoring ventilation and IPPV is generally adjusted to achieve a  $P_{\mathrm{ET}}\mathrm{CO}_2$  of 30-35 mmHg. For longer procedures such as surgery, direct analysis of arterial blood gases is essential.

Pulse oximetry: This can be used to provide a guide to the oxygenation of the patient. This technique measures the percentage of haemoglobin (Hb) that is saturated with oxygen. Due to the shape of the oxygen dissociation curve, a saturation of >95% is required to ensure a  $P_{\rm a}O_{\rm 2}$  >80 mmHg (Figure 20.9). There are many physiological and technical factors that can interfere with pulse oximetry. Detailed discussion of these factors and of the oxygen-carrying capacity of blood is beyond the scope of this chapter but can be found in West (2000). Where possible, arterial blood gas analysis should be performed. It is important to note that pulse oximetry does not assess adequacy of ventilation and that severe hypercapnia can develop despite adequate oxygen saturation.



Due to the shape of the oxygen dissociation curve, a saturation of >95% is required to ensure a  $P_a O_2$  >80 mmHg.

**Body temperature:** Body temperature in animals with CNS disease should be maintained within the normal range (Ruslander, 1992; Ahn, 1995).

- Hypothermia decreases cerebral metabolic rate (CMR) and has been used in human patients as a form of neuroprotection. However, the efficacy of controlled hypothermia has been a contentious issue, due to its inconsistent effect on outcome (Clifton et al., 2002). Furthermore, hypothermia leads to shivering and increased oxygen consumption during recovery, and should be avoided.
- Hyperthermia increases CMR, which increases CBF and can lead to increases in ICP and further reductions in CPP.

It is important to remember that head trauma and intracranial surgery in animals, especially involving the brainstem and hypothalamus, can result in impaired thermoregulation. Close monitoring of temperature in these animals is imperative, and instigation of appropriate therapy should be performed when abnormalities arise. Methods for supporting body temperature are discussed in more detail below.

#### Recovery

The aim of recovery is to achieve a smooth emergence with minimal coughing and straining. Timing of extubation of animals with intracranial disease is a compromise between ensuring that the animal is able to ventilate adequately and maintain normocapnia while preventing a pressor response and coughing.

To minimize the pressor response the same techniques can be used as those described for intubation. Lidocaine administered at a dose of 1 mg/kg i.v. can be useful a few minutes prior to extubation. Hypertension (MABP >130 mmHg; SABP >160–200 mmHg) in the recovery period can be treated by administration of beta-receptor antagonists. Esmolol is the agent of

choice, due to its short duration of action which allows it to be titrated to effect. This agent has been used to blunt pressor response to extubation in humans and is reported to be more effective than other beta blockers (Himmelseher and Pfenninger, 2001). The use of esmolol in small animal neurosurgical patients has not been reported. Dose rates used in cardiovascular disease in dogs and cats include 0.25–0.5 mg/kg by slow intravenous injection or 10–200  $\mu g/kg/minute$  infusion titrated to effect.

# **Analgesia**

Intracranial disease in animals does not appear to cause severe pain, except where trauma is involved. Most animals with intracranial disease can generally be managed with mild analgesics, such as butorphanol or buprenorphine. In the immediate perioperative period, more effective analgesic agents, such as methadone or pethidine, are preferred. Morphine is

generally avoided because of the risk of vomiting, which is associated with significant increases in ICP. For animals with severe pain, such as head trauma patients with multiple injuries, infusions of fentanyl may be useful. Due to the short duration of action of this drug, the infusion rate can be titrated to achieve adequate analgesia and minimal respiratory depression.

Potential complications of opioid administration include bradycardia and associated hypotension as well as respiratory depression and associated hypercapnia. Opioids are also reported to cause pupil dilation in cats and constriction in dogs, which can potentially interfere with neurological assessment. In conscious animals, these side-effects do not appear to be a problem at the low doses used clinically (Figure 20.10). However, these agents should still be used with care, particularly in the depressed or stuporous patient where side-effects are generally exacerbated.

Indication	Agent	Advantages	Disadvantages	Dose regimen
Pre- and postoperative	Butorphanol	Good sedative	Mild analgesia (kappa-agonist) Short duration of analgesia Antagonizes pure mu agonists	0.05–0.4 mg/kg i.v. or i.m.ª
	Buprenorphine	Long duration (6–8 hours)	Mild analgesia (partial mu agonist) Prolonged onset (30–60 minutes)	0.006–0.01 mg/kg i.m. or s.c.ª q8h
-badi bata Shigitan id	Morphine	Potent analgesia (full mu agonist) Can be used as CRI postoperatively	Nausea and vomiting Histamine release with rapid i.v. injection	0.1–0.4 mg/kg i.v. or i.m.ª q2–6h <sup>b</sup> CRI: 0.1 mg/kg/h
	Methadone	Potent analgesia (full mu agonist) Moderate duration of action	Pharmacokinetics in small animals unclear May accumulate with repeated dosing	0.1–0.4 mg/kg i.v. or i.m.ª q2–6h <sup>b</sup>
	Pethidine	Potent analgesia (full mu agonist)	Potent cause of histamine release if given i.v. Pain on i.m. injection Short duration of action	2–5 mg/kg i.m. or s.c. q2–4h <sup>b</sup>
	Fentanyl	Potent analgesia (full mu agonist) Short-acting (10–15 minutes) Suitable for infusion	High doses cause respiratory depression	CRI: 2–5 μg/kg/h Transcutaneous patches: 2–5 μg/kg
Intraoperative	Fentanyl	Potent analgesia (full mu agonist) Short-acting (15 minutes) Suitable for infusion	Marked respiratory depression at doses used intraoperatively Duration of action increases with duration of infusion	Bolus 1–2 μg/kg i.v. q15–20min CRI: 0.2 μg/kg/min
	Alfentanil	Potent analgesia (full mu agonist) Short-acting (5 minutes) Suitable for infusion	Marked respiratory depression at doses used intraoperatively Duration of action increases with duration of infusion	1 μg/kg/min i.v.
	Remifentanil	Potent analgesia (full mu agonist) Very short-acting (1–2 minutes) Easily titrated to effect Duration of action is constant regardless of duration of infusion	Marked respiratory depression at doses used intraoperatively Very rapid recovery: additional analgesia required before stopping infusion	0.2–0.5 μg/kg/min i.v.

Advantages and disadvantages of opioid analgesic agents used for perioperative pain control in dogs and cats with neurological disease. Dose rates commonly used are also provided. <sup>a</sup> For range of doses given, the lower doses are recommended for i.v. administration (where specified) or i.m. injection in depressed animals, and the higher doses for i.m. administration in alert animals or those in pain. <sup>b</sup> Cats may have slower metabolism and may require less frequent administration. CRI = continuous-rate infusion.

# Supportive care

#### Fluid therapy

Fluid therapy is required in the neurological patient to ensure normovolaemia and normotension and to minimize alterations in electrolyte and acid—base balance. Water restriction was previously thought to decrease brain water content but it is now known that the adverse effects of this action on blood viscosity result in decreased oxygen delivery, which stimulates vasodilation and increases CBV and ICP (Cornick, 1992).

Fluid requirements include maintenance plus insensible losses (e.g. panting). In normal animals, maintenance requirements are 2 ml/kg/h (50 ml/kg/day). Animals receiving corticosteroids and osmotic diuretics such as mannitol are polyuric and have higher maintenance requirements; in these animals, rates of fluid administration can be adjusted according to the volume of urine produced. During surgery, dose rates of 10 ml/kg/h are generally used to accommodate for the relative hypovolaemia associated with the vasodilatory effect of anaesthetic agents. Blood loss should preferably be replaced by colloid or blood administration, to limit the volume of fluids administered.

The types of fluid suitable for use in patients with intracranial disease are summarized in Figure 20.5. Hypotonic solutions such as Hartmann's can be used as long as large volumes are not required, as this could increase brain tissue water and ICP (Cornick, 1992). Isotonic crystalloid solutions are the preferred fluids where large volumes are required for rehydration or intraoperatively. Unfortunately, the only isotonic crystalloid solution available in the UK is 0.9% saline, which results in hyperchloraemic metabolic acidosis if administered for prolonged periods. In animals with normal serum electrolyte concentrations, the authors tend to use 0.9% saline intraoperatively and Hartmann's solution for maintenance requirements perioperatively.

Adequacy of fluid therapy can be assessed by measuring CVP and urine output. Urine output is monitored by an indwelling urinary catheter attached to a sterile collection bag. Normal urine output should be 1–2 ml/kg/h. Urine output <1 ml/kg/h may indicate dehydration, particularly if accompanied by high specific gravity (SG). Using urine output to assess the hydration status of a neurological patient is complicated by administration of mannitol and corticosteroids, which results in production of large amounts of dilute urine. In these cases, daily monitoring of bodyweight can be useful.

Use of urinary catheters with closed collection systems (Figure 20.11) not only assists with monitoring fluid balance but also helps keep the animal comfortable and reduces the need for manual expression of the bladder. However, this has to be balanced against the increased risk of developing a urinary tract infection (UTI). Placement of indwelling catheters should be performed using sterile technique. Catheters are then attached to sterile closed collection systems. To prevent tension on the bladder and urethra, the collection system is bandaged to the hindlimb. Where commercial systems are not available, empty drip bags and lines are suitable alternatives. Urinary catheters should

be flushed if urine output decreases to ensure that the system is not blocked with sediment. However, this should be done under sterile conditions as retrograde flushing of the catheter may increase the risk of infection. Many patients that undergo intracranial surgery have minimal neurological signs postoperatively and urinary catheter placement is not necessary.



Closed urine collection system in a dog recovering from spinal surgery. Placement of indwelling catheters should be performed using a sterile technique. Catheters are then attached to sterile closed collection systems. To prevent tension on bladder and urethra, the collection system is bandaged to the hindlimb.

#### Nutrition

Nutrition is extremely important and enteral feeding should be instigated in inappetent animals within 72 hours.

Oesophagostomy tubes (Figure 20.12) are preferred for enteral feeding in animals with intracranial disease, as nasogastric tubes can cause sneezing and an associated increase in ICP. In animals with brainstem lesions resulting in dysphagia and megaoesophagus, gastrostomy tubes are preferred in order to prevent regurgitation and aspiration (Figure 20.13). Feeding should be commenced slowly. It is generally recommended that feeding be initiated at one-third maintenance for the first day, two-thirds on the second day and then full maintenance on the third day. For a detailed description of enteral feeding see Abood *et al.* (1992).



Oesophagostomy tubes are the preferred method of providing long-term enteral nutrition to animals without megaoesophagus.



Gastrostomy tubes are the preferred method of providing enteral nutrition to animals with megaoesophagus.

In animals that are interested in eating voluntarily, water and food are introduced gradually in the post-operative period (small amounts every 1–2 hours) with strict attention to the ability to swallow. Once it has been ascertained that these animals can swallow normally without regurgitation, normal feeding routines can be resumed. If there is any doubt as to whether to feed orally, a chest radiograph will help to determine the

presence or absence of megaoesophagus. This seems to be more common following surgery on the brainstem.

Intravenous fluid therapy is necessary until oral intake has reached recommended maintenance levels. When oral intake is reduced, supplementation with potassium chloride (KCI) is required in order to maintain normal serum potassium levels (3.5–5.5 mmol/l). Concentrations of KCI that can be added to fluids are summarized in Figure 20.14.

To avoid adverse cardiac effects, the rate of KCl administration should not exceed 0.5 mmol/kg/h.

# **Spinal disease**

# Anaesthesia

It is now recognized that many of the principles of anaesthesia for animals with intracranial disease are relevant to animals with spinal disease. Arterial blood flow in the spinal cord is autoregulated in the same manner as CBF to remain constant over a range of blood pressures. In addition, arterial  $\rm CO_2$  has also been shown to be important in regulation of spinal cord blood flow. Considerations for sedating and anaesthetizing patients with spinal disease are summarized in Figure 20.15.

Serum concentration (mmol/l)	Amount KCl added to fluids (mmol/l)	Maximum rate (ml/kg/h)
<2.0	80	TO 6 Children Bankman deligning
2.1–2.5	60	8
2.6–3.0	40	12 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
3.1–3.5	30	15

Guide for potassium chloride supplementation. (Extrapolated from Dibartola, 2000)

Problem	Aetiology	Anaesthetic management	
Pain	Disc herniation, fracture, infection, inflammation Muscle spasm	Analgesia (see Figure 20.10) Muscle relaxants (benzodiazepines)	
Mechanical instability	Fracture Cervical malformation (wobbler) Atlantoaxial subluxation	Careful positioning of animal Support neck during intubation Avoid agents that cause vomiting	
Decreased spinal cord perfusion	Hypovolaemia: dehydration; blood loss Impaired autoregulation in diseased spinal cord: small decrease in blood pressure may oause ischaemia Lesions proximal to thoracolumbar junction cause autonomic imbalance and hypotension	Correct fluid and electrolyte abnormalities before anaesthesia Maintain normotension: Use agents that minimally depress autoregulation Use agents that minimally depress cardiovascular function	
Respiratory insufficiency/failure	Cervical spinal injury: loss of intercostal and diaphragmatic innervation Surgical technique: Sternal recumbency may restrict diaphragm Retraction of trachea during cervical surgery can obstruct airway Potent opioids used for intraoperative analgesia depress ventilation	Pre-oxygenate Monitor adequacy of ventilation: Capnography Pulse oximetry Blood gas analysis Provide assisted ventilation when necessary	

20.15 Considerations for sedation and anaesthesia of patients with spinal disease. (continues)

Problem	Aetiology	Anaesthetic management
Hypothermia	Autonomic imbalance: peripheral vasodilation increases heat loss Surgical exposure	Monitor temperature Active warming: warm water or air blankets
Surgical blood loss	Can be significant if venous sinus is damaged	Quantify blood loss: swabs, suction bottles Transfusion: Blood loss >20% blood volume Haemoglobin concentration <8 g/dl
Myelography	Contrast agent predisposes to seizure activity	Slow injection Lumbar puncture Head elevation after cisternal injection Avoid anaesthetic agents that decrease seizure threshold or have inherent epileptogenic activity

20.15 (continued) Considerations for sedation and anaesthesia of patients with spinal disease.

#### Premedication

Premedication usually involves the use of opioids, with or without the use of agents with sedative or anxiolytic properties. Animals with spinal injury, particularly those that are paralysed, can be very anxious. In these cases, provided the animal is normovolaemic, low-dose acepromazine maleate (ACP) (0.01–0.02 mg/kg i.m.) in combination with opioids can be useful. Some practitioners avoid the use of ACP if myelography is to be performed because of concerns about post-myelographic seizures.

Medetomidine may be useful for sedation and anxiolysis in extremely anxious or fractious animals without cardiac disease and that are normally hydrated. Intramuscular doses as low as 2–5 μg/kg can provide useful sedation when combined with other agents such as opioids or ACP. Medetomidine has the additional benefits of providing analgesia and skeletal muscle relaxation. Medetomidine is reported occasionally to cause vomiting and thus should be used carefully when cervical instability is suspected.

Benzodiazepines are generally poor sedatives in otherwise healthy dogs but provide useful sedation in cats when used in combination with other agents. Midazolam (0.2 mg/kg), in combination with opioids or ketamine, is useful for premedication of cats with spinal disease. Ketamine (3–5 mg/kg i.m.) may also be combined with ACP for premedication in normovolaemic cats with normal renal function. However, as intramuscular injections are painful and can provoke extreme agitation, they are best avoided in cats with unstable spinal disease.

## Induction

Induction is performed with intravenous agents to ensure rapid, controlled induction with minimal struggling.

Selection of an appropriate induction agent is based on similar principles to those described for animals with intracranial disease. The characteristics of intravenous agents and suggested dose rates are described in Figure 20.7. To decrease the dose of the intravenous agent and minimize cardiovascular

depression, concurrent administration of a potent opioid, such as fentanyl, or benzodiazepines can be used during induction.

Intubation should be performed carefully, with adequate support of the head and neck, particularly in animals with cervical injuries.

The animal should be placed on a flat surface or table with its head and neck flat and supported by the table. Intubation is facilitated by use of a laryngo-scope (Figure 20.16). Excessive neck extension should be avoided in dogs with caudal cervical lesions, while excessive neck flexion should be avoided in animals with atlantoaxial subluxation or other cervical fractures.



20.16 Intubation of animals with unstable cervical lesions should be performed with the head supported on a flat surface. The neck should not be overextended or overflexed. Visualization of the larynx is aided by the use of a laryngoscope.

# Maintenance

Maintenance is usually performed with inhalation agents. As autoregulation and  $CO_2$  responsiveness are maintained better with isoflurane than with halothane, isoflurane is the preferred maintenance agent. Nitrous oxide is reported to increase ICP and is avoided in patients with intracranial disease. Whether the same precautions are warranted in animals with spinal cord

injury and compression is not known. Intraoperative analgesia can be provided by infusions of potent mu opioids such as fentanyl, alfentanil and remifentanil (see Figure 20.10).

IPPV is recommended during anaesthesia in the spinal patient for several reasons:

- The detrimental effects of inhalation agents, such as isoflurane, on spinal blood flow regulation can be minimized by maintaining normocapnia
- Surgical access requires that the animal is positioned in sternal recumbency, which can interfere with diaphragmatic excursions and impair ventilation
- The doses of opioid agonists recommended for intraoperative use produce marked respiratory depression, necessitating IPPV.

# Monitoring

During diagnostic imaging and surgery in animals with spinal disease, non-invasive monitoring of cardio-pulmonary function with electrocardiography, oscillometric blood pressure measurement, capnography and pulse oximetry is generally adequate. In animals where cardiopulmonary dysfunction (e.g. cranial cervical surgery; trauma involving multiple organ systems) or excessive blood loss is expected, invasive monitoring is recommended. Monitoring techniques have been discussed in detail above.

# **Analgesia**

Parenteral administration of opioid agents provides the most effective pain relief in animals with spinal disease.

Due to the severity of pain in most animals with spinal disease, analgesia is best achieved with opioid analgesics (see Figure 20.10). Although vomiting is less likely in animals in pain, the use of morphine is generally avoided in animals with cervical injury where violent movements associated with vomiting can cause further injury to an unstable lesion. In addition, recumbent animals that vomit may not be able to clear vomitus from their pharynx and mouth, predisposing to airway obstruction and subsequent aspiration.

Parenteral administration is recommended in the immediate perioperative period. In addition, skin patches that deliver fentanyl transcutaneously may provide a useful adjunct to perioperative analgesia (Figure 20.17). As there is a delay of approximately 12–24 hours in attainment of peak concentrations, the patches should be placed the day before surgery where possible. There is marked individual variation in the serum concentrations achieved; thus, while useful, fentanyl patches should not be relied on as the sole method of providing analgesia.

Non-steroidal anti-inflammatory drugs (NSAIDs) may be used to decrease inflammatory pain. Cyclo-oxygenase inhibitors, carprofen and meloxicam and the mixed lipoxygenase and cyclo-oxgenase inhibitor tepoxalin are registered for perioperative use as these agents do not interfere with platelet function.



20.17 A fentanyl patch placed on the lateral thorax of a dog after spinal surgery. The patch was placed just behind the shoulder blade on the flat part of the lateral thorax. The hair was clipped and the skin cleaned and dried before placement. After placement, the patch was covered with a protective dressing.

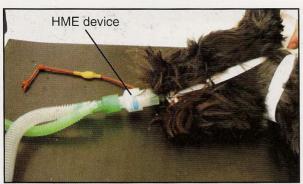
Concurrent administration of NSAIDs and corticosteroids is contraindicated due to increased risk of gastrointestinal ulceration and haemorrhage; thus the use of NSAIDs is best delayed until it has been decided whether the patient will need corticosteroid therapy. To reduce the incidence of gastrointestinal ulceration in animals receiving steroids or NSAIDs, concurrent administration of gastrointestinal protectants is recommended.

Muscle relaxants, such as benzodiazepines (diazepam 0.25 mg/kg orally q8h), may provide useful adjuncts to pain management in patients with *stable* spinal injury by alleviating muscle spasms commonly observed in animals with spinal disease. Skeletal muscle relaxation may be detrimental in animals with unstable spinal lesions as it reduces the splinting effects of the epaxial muscle.

# Supportive care

Fluid balance must be maintained, and intravenous fluid therapy is essential during anaesthesia in all cases. In hypovolaemic animals, volume deficit should be replaced before anaesthesia. As blood loss can be surprisingly high during spinal surgery, the amount of blood on swabs and in suction bottles should be monitored throughout anaesthesia. Blood transfusion is indicated when blood loss is >20% of the circulating blood volume or haemoglobin concentration is <8 g/dl. Smaller amounts of blood loss associated with hypotension can be managed with administration of colloids such as etherified starch (maximum dose 20 ml/kg/24 h).

Heat loss can be a problem, particularly when spinal cord injury causes sympathetic nervous system dysfunction and peripheral vasodilation. Temperature should be monitored during anaesthesia. Warming can be provided during anaesthesia by use of warm waterbeds or air blowers. Heat and moisture exchange devices (Figure 20.18) can be placed between the endotracheal tube and circuit, to decrease heat and moisture loss from the patient.



A humidifying and moisture exchange (HME) device, placed between the patient and the anaesthetic circuit, prevents excessive heat and fluid loss during anaesthesia.

# Perioperative nursing

It is essential that administration of analgesia is continued during the initial recovery period into the post-operative period to ensure a calm, pain-free recovery. In some cases use of low-dose sedatives, such as ACP (0.01–0.02 mg/kg i.m.), may be required in extremely stressed or agitated animals. Analgesia in the immediate postoperative period can be provided by incremental administration of mu agonists or continuous-rate infusions. Morphine and fentanyl have both been used postoperatively as continuous-rate infusions in humans and animals (see Figure 20.10).

Urinary catheters can be important in recumbent animals and in any animal where bladder function may be altered by spinal injury. They are particularly useful in trauma patients with extensive soft-tissue bruising. Catheters should be inserted using a sterile technique and attached to closed collection systems to prevent UTI. Antibiotics should not be used empirically in these patients as their use will encourage development of resistant UTIs. Catheter systems should be used for as short a time as is necessary. (For management of indwelling catheters see above.) Frequent intermittent manual bladder expression or catheterization is an alternative option but is not always possible. Use of drugs to relax the internal and external urethral sphincters can facilitate manual expression (see Chapter 18).

For recumbent animals, padded bedding is essential to prevent pressure sores (Figure 20.19); see also Chapter 24. Non-slip matting and padded kennels also help to reduce injury in ataxic or weak animals that may be unstable when trying to walk.



20.19 Adequate padding is essential to prevent the development of pressure sores in recumbent animals.

# Special considerations for diagnostic procedures

# Myelography

Seizure activity is a well recognized adverse effect of contrast injection. The risk of seizures is influenced by several factors, including: volume and rate of contrast injection; site of injection; size of animal; duration of anaesthesia after injection; and position of animal during injection (Court *et al.*, 1990b). Seizures are more commonly observed after cisternal injection than after lumbar injection. Animals >20 kg in bodyweight are also observed to have a higher incidence of seizures, possibly due to a relatively higher volume of contrast injected (Court *et al.*, 1990b; Barone *et al.*, 2002).

To reduce the risk of seizures, dose rate should be calculated from surface area rather than bodyweight, the speed of injection should be limited and the head should be elevated as soon as the injection is complete, to allow contrast medium to flow away from the head (Court, 1990b). Use of a tilting table allows head elevation while keeping the animal's spine flat on the table. Pharmacological agents that decrease the seizure threshold should be avoided. ACP, ketamine and medetomidine are reported to decrease seizure threshold (Court, 1990a; Rhoney, 2001) and it is recommended that these agents are not used in animals undergoing myelography. Seizures have been reported to occur up to 6 hours after injection of contrast medium, and thus animals should be closely monitored during this time. If seizures occur, administration of diazepam (0.2-0.5 mg/kg i.v.) is recommended.

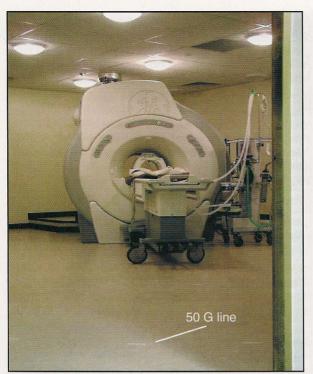
Cardiopulmonary side-effects have also been observed during or immediately after injection of contrast medium, including apnoea, tachypnoea, bradycardia, tachycardia, arrhythmias, hypotension and hypertension (Court *et al.*, 1990b; Barone *et al.*, 2002). Some of these effects are associated with discomfort or pain of injection and can be minimized by slow injection of contrast and ensuring adequate depth of anaesthesia during injection. To detect these problems, careful monitoring of cardiopulmonary function is necessary during myelography.

#### Magnetic resonance imaging

The main considerations for anaesthetizing patients with spinal and intracranial disease are described above. In addition there are several important considerations unique to anaesthetizing a patient within a magnetic field (Menon, 2001).

Ferromagnetic objects can become projectile and may result in injury to the patient or personnel within the scanning room. It is essential that these objects remain outside the 50 gauss line (Figure 20.20).

Non-ferromagnetic objects and implants have the potential to distort or degrade the quality of the image. Anaesthetic machines are required to be as close to the patient as possible to minimize the length of anaesthetic circuits, and should be composed of non-ferromagnetic materials.



Ferromagnetic objects can become projectile and may result in injury to the patient or personnel within the scanning room. It is essential that these objects remain outside the 50 gauss (50 G) line.

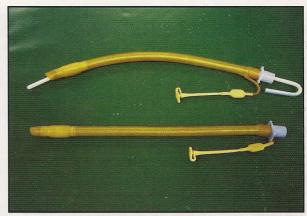
Non-ferromagnetic objects within a magnetic field (e.g. ECG leads) have the potential to induce electric currents, leading to heating and burns. The risk of burns can be minimized by insulating the wires, separating the wires from skin by padding, avoiding large loops of wire that allow induction of currents, and applying sensors as far away as possible from the imaged area.

Monitoring the anaesthetized patient during MRI has inherent limitations. Equipment used for monitoring must be MRI-safe and ideally MRI-compatible. MRI-compatible equipment has been shown to be safe, not to significantly reduce the diagnostic quality of the image and not to have its operation affected by the scanning procedure. At present, MRI-compatible equipment is available that allows distant monitoring of animals during the procedure. Where cost is limited, some monitoring equipment such as capnography and oscillometric methods of blood pressure measurement can be used if the electrical components are beyond the 50 gauss line.

# Cerebrospinal fluid collection

Collection of CSF may be performed by cisternal or lumbar puncture (see Chapter 3). Cisternal puncture requires neck flexion; this can kink the endotracheal tube, causing respiratory obstruction, and also obstruct the jugular veins, impairing venous drainage and contributing to increased ICP. Positive pressure ventilation is essential during cisternal puncture to ensure adequate ventilation and normocapnia.

Endotracheal tubes reinforced with coiled wire resist kinking (Figure 20.21) and can be used to



Wire-reinforced endotracheal tubes can be used to prevent airway obstruction caused by neck flexion, which is required for CSF collection and cisternal myelography. As these tubes are very flexible, the use of a malleable stilette can assist placement. Use of these tubes is prohibited in animals undergoing MRI.

prevent airway obstruction when the neck is flexed for collection of CSF. However, as these tubes contain metal, they are not suitable for use in animals undergoing concurrent MRI.

In animals with increased ICP, collection of CSF carries the risk of herniation. When sampling is essential for diagnosis and treatment of the animal, reducing arterial CO<sub>2</sub> to 30 mmHg by hyperventilation during the sampling period may reduce the risk of cerebral herniation.

# **Neuromuscular disease**

Animals with neuromuscular disease (NMD) generally present with localized or generalized weakness, but some peripheral NMD can present with skeletal muscle rigidity such as myotonia. Considerations for anaesthetizing these patients are summarized in Figure 20.22.

## Anaesthesia

#### Sedation

Heavy sedation is usually avoided in animals with NMD. For diagnostic procedures unable to be performed while the animal is conscious, anaesthesia is preferable to heavy sedation as it allows the airway to be protected and the animal to be ventilated and oxygenated.

Light sedation with an anxiolytic, such as ACP (0.01–0.02 mg/kg i.m.), may be warranted in extremely anxious animals, provided the animal is normovolaemic. Sedative agents such as benzodiazepines and alpha-2 agonists produce skeletal muscle relaxation, which can exacerbate respiratory dysfunction and upper airway obstruction. These agents are best avoided in animals with neuromuscular weakness. In contrast, these agents can be useful in animals with tetanic NMD.

Problem	Cause	Anaesthetic management
Dehydration	Weakness and recumbency limit access to water and food Regurgitation, if present, will exacerbate losses	Correct fluid and electrolyte abnormalities before anaesthesia
Aspiration	Dysphagia and/or megaoesophagus Decreased or absent upper airway reflexes	Conscious chest radiographs will help identify presence of megaoesophagus Rapid induction in sternal recumbency, head elevation and cricoid pressure until intubation with cuffed endotracheal tube Select short-acting agents to allow rapid recovery to pre-GA function as soon as possible
Pneumonia	Aspiration Recumbency → pulmonary atelectasis	Chest radiographs Preoperative stabilization with antibiotics
Inadequate ventilation	Respiratory muscle weakness	Assisted ventilation Monitor adequacy of ventilation using capnography and/or blood gas analysis
URT obstruction	Laryngeal paralysis Laryngeal spasm (tetanus)	Anaesthetize and intubate Tracheostomy may be required until recovery of airway function
Hypoxaemia	Respiratory muscle weakness and recumbency predispose to decreased lung volume and atelectasis Pneumonia	Pre-oxygenate Use 100% oxygen during anaesthesia Monitor oxygenation with pulse oximetry and blood gas analysis Provide oxygen supplementation by nasal tube, mask oxygen cage perioperatively
Hyperthermia	Laryngeal paralysis and respiratory muscle weakness reduce efficiency of panting	Passive cooling: fans, clip animals, wet coat with water/alcohol Monitor temperature closely
Hypothermia	Inability to shiver	Passive warming: warm fluids, warm air blankets, heat lamps, incubators (small animals) Monitor temperature closely

20.22

Considerations for sedation and anaesthesia in patients with peripheral nervous system disease. URT = Upper respiratory tract.

#### Premedication

Premedication in NMD animals is usually limited to opioid analgesics. In extremely anxious animals, judicious use of sedatives may be needed to allow a smooth stress-free induction.

#### Induction

Pre-oxygenation should be performed prior to induction when possible. Intravenous agents with rapid onset of action, such as propofol and thiopental, are preferred for induction as this provides rapid intubation of the airway and smooth induction with minimal struggling and rapid recovery. Propofol can also be administered to effect in non-sedated or minimally sedated animals without risk of excitement. When there is a risk of regurgitation, intubation is performed with the animal supported in sternal recumbency. Cricoid pressure is applied until the endotracheal tube is placed and secured in the airway with an inflated cuff (Figure 20.23). The pharynx, oesophagus and stomach should then be suctioned to decrease the risk of aspiration during and immediately after anaesthesia.

#### Maintenance

Volatile agents such as isoflurane or sevoflurane are preferred for maintenance as they are eliminated rapidly at the end of the procedure, allowing rapid recovery of airway reflexes and respiratory function. Agents are delivered in 100% oxygen when concurrent pulmonary



To minimize the risk of aspiration during induction of anaesthesia in animals with suspected megaoesophagus, the animal is maintained in sternal recumbency with the assistant providing cricoid pressure (firm but gentle pressure on ventral larynx) until the endotracheal tube is placed and secured and the cuff inflated.

pathology is suspected or confirmed. Assisted ventilation is recommended and adequacy of ventilation should be monitored using capnography or blood gas analysis.

#### Recovery

Prior to recovery, suction of the oesophagus and pharynx is useful in animals with megaoesophagus to remove the contents so that they are not regurgitated

and aspirated during recovery. The animal is best positioned in sternal recumbency to maximize respiratory function. Extubation is performed as late as possible, to ensure that upper and lower respiratory muscle function is adequate. Ideally the endotracheal tube should be removed gently with cuff inflated, so that any secretions that have accumulated above the cuff during anaesthesia are pulled into the pharynx, where they can be swallowed. Should vomiting or regurgitation occur, the animal's head is positioned over the edge of the table to allow contents to flow out of its mouth. If the animal is sufficiently sedated, the pharynx and mouth may be cleared by suctioning and swabbing.

# **Neuromuscular relaxation**

In animals with NMD, requiring surgery for other reasons, neuromuscular relaxation may be required in order to improve surgical accessibility. Non-depolarizing agents can be used in these animals but extreme care is required, as prolonged duration of skeletal muscle weakness can occur. Depolarizing agents should be avoided.

Administration of relaxants should be performed incrementally, with appropriate monitoring of neuro-muscular function and ventilation. Short-acting neuro-muscular blockers such as atracurium or vecuronium, at one-tenth of the usual dose, are preferred agents. Infusions allow finer control than boluses, and overdose can be avoided by titrating these agents to effect. Description of the techniques available to monitor neuromuscular relaxation is beyond the scope of this chapter but a detailed discussion can be found in standard anaesthetic texts, such as Hall *et al.* (2001).

#### Analgesia

Peripheral NMD may or may not be painful, depending on cause. Electrodiagnostics and muscle and nerve biopsies commonly performed in animals with peripheral NMD necessitate use of analgesia in most cases.

Opioid analgesics provide good pain relief in the perianaesthetic period. Due to a reduced ability to protect the airway in many neuromuscular patients, agents that predispose to vomiting, such as morphine, are best avoided. Methadone and pethidine are suitable alternatives and, when given at clinical doses, are associated with minimal respiratory depression. Butorphanol (0.2–0.4 mg/kg i.m.) is less effective as an analgesic but has good sedative qualities that make it a useful premedicant in animals that do not require potent analgesia.

NSAIDs are useful for controlling inflammatory pain. It is recommended that NSAIDs are withheld until the decision has been made as to whether the patient will require treatment with corticosteroids.

#### Supportive care

#### Perioperative nursing

Padded bedding and frequent turning (every 4–6 hours) are important in recumbent animals, to prevent pressures sores and limit the severity of pulmonary atelectasis. A urinary catheter with a closed collection bag can be placed to help to keep the patient comfortable and clean.

Nutrition is important and enteral nutrition should be instigated in any animal that is not eating adequately. Nasogastric feeding tubes can be placed in conscious animals and are suitable for short-term enteral nutrition. Oesophagostomy tubes are well tolerated for long-term enteral nutrition and this is the preferred method for cats. However, in animals with dysphagia or megaoesophagus the safest method of feeding is via a gastrostomy tube, which can be placed surgically via laparotomy or percutaneously with endoscopic guidance.

Intravenous fluid therapy is necessary until oral intake has reached recommended maintenance levels. Animals treated with corticosteroids are polyuric and may have higher maintenance fluid requirements than normal animals. Supplementation of electrolytes such as potassium is recommended when oral intake is reduced. Electrolyte and fluid balance should be monitored.

#### Thermoregulation

Animals with neuromuscular disease have an impaired ability to thermoregulate. In cold climates, the inability to shiver can lead to hypothermia (Ahn, 1995). In hot climates, the inability to pant adequately can lead to hyperthermia (Ruslander, 1992). As a result, the temperature of these animals needs to be monitored closely at all times.

To warm animals, passive heating with heat lamps, hot-air blankets and warmed intravenous fluids is preferred. For small dogs and cats, incubators are also useful. Direct heat should be avoided, as poor circulation prevents heat dissipation and can lead to serious burns. In severely hypothermic animals (<32°C), more aggressive methods of warming may be required, including gastric lavage with warm water, warm-water enemas or peritoneal lavage with warm sterile saline. For hypothermic animals that are also hypovolaemic or dehydrated, aggressive warming should be avoided as warming causes peripheral vasodilation and worsening of hypovolaemia. In these animals, warming should be performed slowly and in conjunction with appropriate fluid therapy, as previously discussed. Warming should cease when the rectal temperature reaches 1°C below target body temperature (37.0°C) to prevent excessive increases in temperature and hyperthermia.

To cool animals, passive cooling with fans and the shaving of hairy dogs is generally effective. For severe hyperthermia (>42°C), intravenous fluid therapy should be instigated. The animal can be sprayed with cool water over the neck and medial surfaces of the upper limbs. Cooling peripherally is not recommended as blood vessels are more prone to vasoconstriction, which predisposes to 'sludging' of the blood and disseminated intravascular coagulation. It is important to remember that aggressive and rapid cooling also results in peripheral vasoconstriction, which increases the risk of the animal developing disseminated intravascular coagulation. Thus, the temperature should be monitored closely; cooling should cease and the animal be dried when rectal temperature reaches 1°C above target temperature (39.5°C), to prevent excessive reduction in body temperature and hypothermia.

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# **Principles of neurosurgery**

# Beverly K. Sturges and Peter J. Dickinson

# Introduction

Treatment options for neurological diseases include medical and/or surgical intervention. The decision to operate involves the assessment of many factors, some of which may be specific for a particular disease. In some patients, serial neurological examinations and monitoring of response to non-surgical treatment are essential in determining whether surgery is indicated.

The purpose of this chapter is to provide an overview of common neurosurgical procedures, general and specific indications for their use, and the complications that may result. Detailed description of specific neurosurgical procedures is beyond the scope of this chapter; the reader is directed to Wheeler and Sharp (1994), Seim (1997) and Sharp (2002) for reviews of these procedures. Procedures for treating vertebral fractures and luxations are described and illustrated in the BSAVA Manual of Small Animal Fracture Repair and Management.

# **Indications for neurosurgery**

#### **General indications**

- The surgical procedure has been shown to have a significantly better clinical outcome than medical treatment.
- The disease is unresponsive or no longer responsive to medical therapy (e.g. progressive neurological deterioration secondary to elevated intracranial pressure resulting from a spaceoccupying tumour, unresponsive to corticosteroid and osmotic diuretic medications).
- The clinical signs are severe or rapidly progressive (e.g. an animal presenting with acute herniation of an intervertebral disc and loss of deep pain perception)
- There is vertebral column instability.

The clinical response to medical *versus* surgical treatment varies over time. Palliation of clinical signs with medical therapy may be effective in the short term but surgical intervention, such as resection or debulking of tumours, may result in an improved long-term outcome. The risks and benefits of surgery, together with the effects of delaying surgery to pursue medical treatment, must be assessed for each individual case.

When determining whether or not to pursue surgery, it is essential to have an accurate neuroanatomical localization. Lesions identified outside the region of localization may not be clinically significant, and treatment may not be indicated. Lesions found within the region of localization should be defined anatomically as completely as possible, to allow precise surgical planning.

# Neurosurgical emergencies

Indications for emergency surgical referral are based on the presence of severe and/or progressively deteriorating neurological signs. For appropriate medical treatment prior to referral, e.g. cardiovascular stabilization, oxygen therapy, hyperosmolar treatment, the reader is referred to Chapter 19 and to the BSAVA Manual of Canine and Feline Emergency and Critical Care. The most common neurological injuries that may require emergency surgery include acute spinal cord and brain injury.

# Acute spinal cord injury

#### Causes include:

- Vertebral fracture/luxation
- · Acute, traumatic disc herniation
- Haemorrhage/haematoma
- Decompensating neoplasia

The presence of any or all of the following clinical signs may warrant the need for immediate surgical intervention:

- · Rapid progression from paresis to paralysis
- Acute paralysis
- Loss of conscious pain perception
- Schiff–Sherrington posture
- Hypoventilation
- Suspected vertebral column instability.

#### Acute brain injury

#### Causes include:

- · Intracranial haemorrhage/haematoma
- Depressed skull fractures
- Decompensating neoplasia
- Rapidly progressing intracranial oedema/ hypertension.

The presence of any or all of the following clinical signs may warrant the need for immediate surgical intervention:

- Progressive deterioration in mental status
   (e.g. obtundation progressing to stupor or coma)
- Progressive loss of brainstem reflexes (e.g. pupillary light reflexes, palpebral reflexes, gag reflex)
- Decerebrate or decerebellate posture
- Abnormal ventilatory patterns.

# **Common procedures**

- Decompression involves removal of part of the bony calvarium or vertebra and/or removal of space-occupying masses to alleviate ongoing compression of neural tissue.
- Fenestration is the creation of an opening in the intervertebral disc by removal of a section of the annulus fibrosus, to allow the removal of nucleus pulposus (pulpectomy).
- Realignment, stabilization and/or fusion of one or more vertebrae is indicated when vertebral column instability is present secondary to fracture, luxation or malformation/malarticulation.
- Mass resection may involve the removal of any infiltrative or compressive tissue including: disc herniation; neoplasia; inflammatory/infectious granulomas; haematomas; bony proliferation; and hypertrophied soft tissues.
- Exploratory surgery and biopsy is indicated when
  a definitive diagnosis cannot be determined by
  other neurodiagnostic procedures such as
  advanced imaging, CSF analysis or
  electrophysiology. Biopsy may be undertaken
  during decompressive or excisional procedures,
  and can provide valuable information relating to
  drug sensitivity in infectious conditions such as
  discospondylitis. It is commonly used to
  determine the aetiology of peripheral nerve and
  muscle disorders (see Chapter 6).

# Selection of a neurosurgical procedure

Factors to consider when selecting a neurosurgical procedure are:

- Neuroanatomical location of the lesion along the neuraxis, as well as the exact location of the pathological process (e.g. whether compression is ventral, lateral or dorsal to the spinal cord)
- Intended goal (e.g. decompression, excision, biopsy)
- Regional anatomy and neuroanatomy
- Extent of the lesion and the amount of exposure needed.
- Extent of removable bone and the impact this may have on regional biomechanical function and stability (especially if preoperative instability is present)
- · Neurological status of the patient.

# **Equipment and setting**

Neurosurgery should be performed in a setting where intensive monitoring is available, both during the anaesthetic procedure and in the immediate post-operative period (see Chapter 20). An anaesthetist should be present throughout the procedure and blood products for transfusion should be available. In addition to routine orthopaedic surgical instruments, the neurosurgeon should have available a high-speed pneumatic or electric drill and burrs, monopolar and bipolar cautery, haemostatic sponge/agents and suction. Additionally, an ear hook and spoon, dural hook and/or an array of microdissection instruments may be needed.

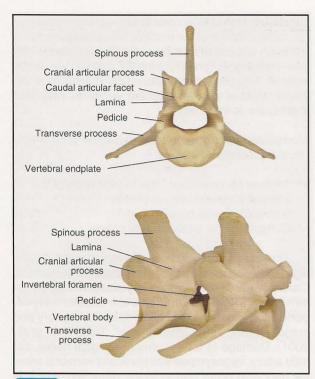
# **Spinal surgery**

Figure 21.1 defines some terms commonly used in spinal surgery. Vertebral anatomy is illustrated in Figure 21.2.

Term	Definition	
Laminectomy	The excision of lamina, or the dorsal portion of the vertebral arch	
Hemilaminectomy	Removal of one half of the vertebral arch (the lamina, articular process and pedicle on one side)	
Dorsal laminectomy	Removal of the spinous process and the laminae of the vertebral arch	
Deep dorsal laminectomy	Extension of the dorsal laminectomy ventrally to include the articular processes uni- or bilaterally with or without pediculectomy	
Continuous dorsal laminectomy	Extension of the dorsal laminectomy cranially or caudally to include multiple vertebral arches	
Pediculectomy	Removal of the pedicle, or the portion of the vertebral arch ventral to the articular processes	
Facetectomy	Removal of an articular process/facet	
Foramenotomy	Enlargement of an intervertebral foramen	
Fenestration	Surgical creation of an opening in the intervertebral disc	
Ventral slot	Slot-like opening created ventrally through the intervertebral disc and cranial and caudal endplate in the cervical region	
Spinal stabilization	The process of removing all motion between adjacent vertebrae by the application of various metallic/synthetic implants, bone cement and/or bone grafts	
Laminectomy membrane	A constrictive, fibrotic, usually hypertrophied, cicatricial tissue covering the region of a previous laminectomy site.	

21.1

Terms commonly used in spinal surgery.



21.2 Vertebral anatomy.

#### Indications

The most common indications for spinal surgery in dogs and cats are:

- Degenerative disc disease
- · Caudal cervical spondylomyelopathy
- Degenerative lumbosacral stenosis
- Trauma
- Neoplasia.

Less commonly encountered indications for spinal surgery are:

- Congenital/acquired malformations (e.g. atlantoaxial instability, synovial cysts, scoliosis)
- Infectious disease (e.g. spinal empyema, abscess, discospondylitis)
- · Epidural/intradural haemorrhage.

#### General complications

The major technical complications associated with spinal surgery are:

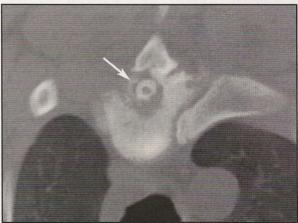
- · latrogenic trauma to neural tissues
- Intraoperative haemorrhage (resulting in hypotension, anaemia or haematoma)
- Spinal vasculature compromise
- Vertebral column instability
- · Excessive scar formation.

The majority of these complications can be treated if they are recognized as they occur and appropriate measures are taken promptly. However, iatrogenic trauma of neural tissue and compromise of local vascular supply are complications that are not easily

rectified. Meticulous surgical technique and a thorough knowledge of regional anatomy are essential to a positive outcome.

In the immediate postoperative period (24–48 hours), inadequate patient confinement can lead to ongoing haemorrhage, haematoma formation and compression of neural elements. This also is the time when recumbent patients, especially those on opioid drugs, can aspirate and may develop pneumonia. In addition to postoperative pain, the neurological status of most patients is often temporarily worse following surgery.

Exuberant regrowth of bone, leading to compression of neural structures and recurrence of neurological signs, is a complication of laminectomy performed in immature animals (Figure 21.3). In the authors' experience this is most commonly a problem with continuous dorsal laminectomies in the cervical region. When compressive bony regrowth occurs another operation may be indicated if conservative treatment is ineffective and the patient continues to deteriorate.



Transverse post-contrast CT-myelogram image of a Rottweiler cross-breed taken at one year of age. Apparent spinal pain and non-ambulatory paraparesis caused by congenital vertebral stenosis was diagnosed at 6 months and treated by surgical decompression from T2-T5. The puppy recovered well and returned to normal activity until a year of age when he represented with signs of back pain and moderate paraparesis. Marked bony regrowth is apparent over the previous laminectomy site (arrowed). The puppy became non-ambulatory a few weeks later, at which time a hemilaminectomy was done over the previous surgical site. The dog recovered well with no further problems.

Similar potential complications apply for subsequent procedures in the same region. Additionally, altered anatomy, muscle fibrosis and scar tissue in the region of the previous surgical site can be problematical. By virtue of the fact that the neural tissue has sustained a second injury, the potential for recovery may not be as complete as with the initial event.

Bladder dysfunction and urinary tract infection are common problems in any patient with neurological disease, particularly those with spinal cord dysfunction. Appropriate bladder management together with excellent nursing care, frequent patient assessment and physical therapy is paramount to a positive outcome following neurological surgery (see Chapter 24).

# Cervical spinal surgery

#### Ventral cervical decompression (ventral slot)

The main indications for a ventral approach to the cervical spine include: removal of herniated disc material; cervical disc fenestration/biopsy; and cervical vertebral stabilization. There is minimal soft tissue and bony dissection with this approach, resulting in minimal postoperative morbidity and an early return to comfort and function (Figure 21.4). The window or 'slot' created by the surgeon is directly on the midline, and is particularly useful for removing disc material located in the ventral aspect of the vertebral canal. Removal of larger ventral extradural masses, intradural/intramedullary masses or lesions not primarily on the ventral midline should not be attempted because exposure of the spinal cord is very limited and complications are potentially life-threatening. The ventral slot procedure may be combined with cervical vertebral stabilization (fusion) and distraction when dynamic instability is present.

The primary disadvantage of the ventral slot is the limited exposure the surgeon has to the vertebral

C5 C6

# 21.4

(a) Ventral slot at C5-6, illustrating the limited visualization of the ventral aspect of the spinal cord. Ventral lesions or lesions just lateral to the midline are best treated by this approach. (b) Lateral myelogram of a herniated C6-7 disc in an 11-year-old female spayed Golden Retriever. The dog presented with acute onset cervical pain and non-ambulatory tetraparesis. There is marked deviation of the spinal cord dorsally and narrowing of the intervertebral disc space. Removal of the herniated disc material through a ventral slot resulted in resolution of all clinical sians



canal. If disc material or other space-occupying masses are located lateral to the midline, full decompression is generally not achieved without creating an excessively wide opening and predisposing the patient to vertebral column instability and subluxation (Lemarie *et al.*, 2000). Ventral slots in adjacent vertebrae may also predispose to instability.

**Complications:** Common complications seen in ventral slot procedures include:

- Profuse haemorrhage, due to laceration of the internal vertebral venous plexus
- · latrogenic spinal cord trauma
- Collapse of the intervertebral space.

These may manifest as worsening neurological signs, cervical pain and/or thoracic limb lameness. Cardiac arrhythmias, respiratory compromise, hypotension and Horner's syndrome are uncommonly reported complications of cervical spinal cord injury and surgery (Clark, 1986; Stauffer *et al.*, 1988; Beal *et al.*, 2001). Damage to the recurrent laryngeal nerve, carotid artery, vagosympathetic trunk and vertebral arteries may also occur during tissue retraction, which is required to expose the ventral aspect of the cervical spine. Retraction and trauma to the trachea, although uncommon, may result in subsequent tracheal collapse, particularly in animals with underlying clinical or subclinical tracheal disease prior to surgery.

#### **Dorsal cervical laminectomy**

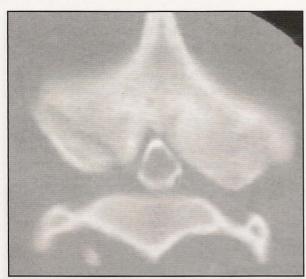
This approach is indicated when greater exposure of the vertebral canal and/or spinal cord is required and is particularly useful when:

- Lesions affect the dorsal and dorsolateral aspects of the spinal cord and vertebral column
- Multiple ventral compressive lesions are present
- Intramedullary tumours and congenital or acquired conditions (e.g. syringohydromyelia and dorsal spinal arachnoid cysts) need to be approached for biopsy, resection or marsupialization.

Preservation of articular processes is essential to maintain as much vertebral column integrity as possible. The laminectomy can be extended cranially and caudally in a continuous fashion over several vertebrae. Careful palpation of the floor of the vertebral canal is possible from this approach. Dorsal laminectomy at C1 is possible; however, hemidorsal laminectomy is preferred at C2 and C2–3 (Figure 21.5) in order to maintain the integrity of the attachment of the nuchal ligament.

Additional lesions accessible by this approach include:

- Large ventral extradural compressions that cannot be removed via a ventral slot
- Laterally located extruded disc material
- · Nerve root tumours
- Spinal cord and vertebral column tumours.



Transverse CT-myelogram image obtained from an 18-month-old English Mastiff, illustrating bilateral osseous lesions associated with the articulations at C2-3. The lesions are causing marked bilateral compression of the cervical spinal cord and are amenable to treatment with surgery.

Sufficient surgical access may require extension of the laminectomy laterally and ventrally (including partial facetectomy) and/or enlargement of the intervertebral foramen (foraminotomy). In addition, osseous and soft tissue stenoses, such as those created by synovial cysts, may be effectively removed by drilling away the inner lamina. The resultant widening of the vertebral canal also allows for decompression of neural tissue.

The main disadvantage of the dorsal cervical approach is the extensive soft tissue and bony dissection, especially in large and giant-breed dogs, where the depth of the surgical approach adds to the difficulty in visualization.

#### Complications:

- Profuse haemorrhage can result from soft tissue dissection as well as laceration of the internal vertebral venous plexus. This can be potentially life-threatening, especially when operating in the rostral cervical region (C1–3).
- Ongoing postoperative haemorrhage, haematoma formation leading to secondary spinal cord compression, and hypoventilation are serious complications that may require further surgery and/or mechanical ventilation.
- Longer operating times, especially with continuous dorsal laminectomies, damage to the underlying spinal cord and slower return to function compared to ventral cervical procedures, are also considerations.
- Potential vertebral column instability and/or the formation of epidural scarring, in addition to the development of a clinically significant laminectomy membrane, are potential long-term complications leading to recurrence of neurological signs.

 Extensive soft tissue dissection predisposes to postoperative seroma formation, particularly in active patients.

#### Lateral cervical laminectomy

Lateral approach to the cervical spine provides the best visualization of the lateral aspect of the:

- Intervertebral disc
- Spinal cord
- Nerve root
- Proximal portion of the peripheral nerve as it exits the intervertebral foramen (Lipsitz and Bailey, 1995).

This is a technically challenging approach and should only be attempted by experienced neurosurgeons. Lateral cervical laminectomy is the best approach for resection of tumours of peripheral nerve that have invaded the spinal cord, especially in conjunction with amputation of the affected thoracic limb. This approach is also useful for resection of tumours of the spinal cord (e.g. meningioma) that exit the intervertebral foramen alongside the vertebral artery, vein and nerve, as well as removing laterally herniated disc material.

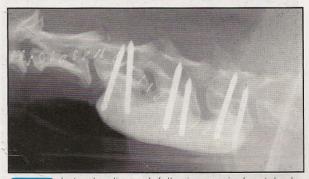
**Complications:** The primary complications include: difficulty in accurate lesion localization; and profuse haemorrhage from vertebral arteries and/or internal vertebral venous plexus disruption.

#### Cervical vertebral stabilization

The primary indications for cervical vertebral stabilization are:

- · Repair of cervical vertebral fracture/luxations
- Cervical vertebral fusion with or without distraction for the treatment of dynamic forms of caudal cervical spondylomyelopathy (in largebreed dogs)
- Atlantoaxial instability.

Surgical stabilization may also be indicated following a ventral slot procedure where the slot is excessively large or instability is anticipated, e.g. in large- or giant-breed dogs (Figure 21.6).



Lateral radiograph following cervical vertebral stabilization for treatment of cervical vertebral spondylomyelopathy and instability at C4–5 and C5–6 in a 5-year-old female spayed Dobermann Pinscher.

# Chapter 21 Principles of neurosurgery

Implants placed in the vertebral bodies provide superior stabilization compared to implants applied to the spinous processes or articular processes or facets. In the authors' opinion, the use of pins or screws and polymethylmethacrylate (PMMA) adhesive is the technique of choice for cervical vertebral fracture or luxation. Many surgical procedures have been described to accomplish distraction and stabilization of dynamic compressive lesions in caudal cervical spondylomyelopathy. These include:

- Ventral slot procedure, with or without stabilization (using pins and PMMA)
- · Vertebral body plating
- · Inverted cone decompression technique
- · Metal washers and screws
- · Polyvinylidine spinal plates
- Harrington rods
- Dorsal laminectomy
- PMMA vertebral body plugs
- External fixators.

Meta-analysis comparing the various approaches have not identified one to be superior over another (Jeffery and McKee, 2001). The ventral approach to the cervical spine provides good visualization of cervical vertebral bodies for accurate realignment, with minimal trauma to soft tissues. Dorsal and ventral approaches for the repair and stabilization of the atlantoaxial (AA) joint have been described in the literature; however, most surgeons agree that ventral repair results in superior fixation.

Complications: Complications unique to the application of implants to the cervical vertebral bodies may result from lack of visualization of the spinal cord and nerve roots during implant placement. The surgeon must be comfortable with three-dimensional visualization of these structures, based on the unique landmarks of the ventral aspect of each cervical vertebra, when placing pins, screws, etc.

- Laceration of vertebral arteries, spinal nerves/ nerve roots and trauma to the spinal cord are the major complications of implant placement.
- Implant failure may occur due to pin migration or inadequate size of implants/PMMA. The use of positive profile-threaded pins significantly reduces pin migration. PMMA infection rarely occurs and is treated by removal of the implant.
- Stabilization of vertebrae, particularly in the caudal cervical region, may predispose to development of a second lesion involving adjacent disc spaces ('domino' lesion) (Jeffery and McKee, 2001).
- Difficulty in swallowing and oesophageal dysfunction as a result of the cement mass are rare complications.

Complications relating to atlantoaxial stabilization vary considerably depending on surgical technique and expertise.

- Improper pin placement due to the lack of visualization of neural structures and fracture of vertebrae during pin/screw placement are potential complications of atlantoaxial stabilization, especially in miniature breeds, which frequently have congenitally malformed vertebrae.
- Placement of pins into the cranial cervical spinal cord, brainstem, atlanto-occipital joints or C1 spinal nerves are serious complications that can lead to vestibular signs, respiratory compromise (requiring assisted ventilation), severe neck pain and/or permanent paralysis.
- Dorsal fixation techniques have been associated with an increased incidence of implant failure and respiratory compromise.

#### Cervical disc fenestration

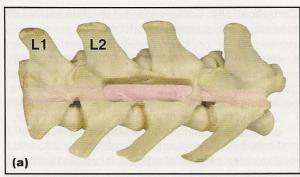
Chondrodystrophic breeds with degenerative disc disease can benefit from cervical disc fenestration. This may be done at the time of decompressive surgery or prophylactically when there is radiographic, CT or MRI evidence of degenerative disc disease. Cervical disc fenestration is not generally recommended for medium- and large-breed dogs with degenerative disc disease because of the possibility of creating vertebral instability.

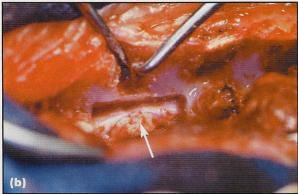
#### Thoracolumbar spinal surgery

#### Hemilaminectomy

This is the best approach for most pathological conditions affecting the thoracolumbar vertebral column, spinal cord and nerve roots. It is essential that the lateralization of the lesion be known prior to this surgical procedure since the contralateral aspects of the spinal cord, nerve roots, and ligamentous and osseous structures are not visualized from this approach. Hemilaminectomy allows good visualization of the ventral and lateral aspects of the spinal cord and nerve roots (Figure 21.7). The stability of the vertebral column is not affected significantly, since the spinous process and associated ligamentous structures, as well as the contralateral articulations, are maintained.

- The majority of clinically significant acute and chronic disc protrusions and extrusions are best treated in this manner.
- This approach also allows easy access to the lateral aspect of the disc for fenestration.
- Extradural and intradural space-occupying lesions in the ventral and lateral aspects of the canal are also best approached by hemilaminectomy, which can be extended cranially, caudally or dorsally to allow for more complete visualization and/or excision of the mass.
- Progressive swelling of the spinal cord can be addressed quickly by extension of the laminectomy cranially and caudally.
- Removal of bony fragments and haematomas secondary to trauma (vertebral fracture/ luxations) and of migrating foreign bodies (grass





(a) Thoracolumbar hemilaminectomy illustrating the visualization of the lateral aspect of the spinal cord. Lesions located ventrally, laterally and dorsolaterally are best treated by this approach.
(b) Intraoperative photograph of a hemilaminectomy in a dog with an acute disc herniation. There is marked deviation of the spinal cord dorsally due to the extruded disc material (arrowed).

seeds, bullets), as well as exploratory/biopsy procedures of the lateral or ventral spinal cord and nerve roots, are also routinely performed via hemilaminectomy.

**Complications:** Complications associated with thoracolumbar hemilaminectomy are uncommon. The major intraoperative complications of hemilaminectomies performed in this region include:

- · latrogenic spinal cord injury
- Nerve root trauma
- · Haemorrhage/haematoma.

Vertebral column instability may be a concern in situations where the laminectomy is extended for more than three vertebral lengths (affecting three or more adjacent articulations) or in active large-breed dogs. Weakening or fracture of the spinous processes may occur if the laminectomy is extended too far dorsally.

# **Dorsal laminectomy**

Indications for dorsal laminectomy in the thoracolumbar region of the spine are the same as those for the cervical region. Occasionally fractures of the thoracolumbar region are approached via dorsal laminectomy, allowing fragment removal and decompression. Instability is a particular concern following dorsal laminectomy of the thoracic or lumbar vertebrae. Bilateral loss



Lateral myelogram of a 6-month-old German Shepherd Dog with dorsal compression of the spinal cord at T5, secondary to a vertebral osteochondroma. The mass was resected via a dorsal laminectomy and the vertebral column stabilized using pins and PMMA. See Figure 21.9 for a later complication.

of articular facets and/or loss of the interspinous ligament can result in significant vertebral column instability and subsequent luxation (Figure 21.8).

#### Thoracolumbar vertebral stabilization

Vertebral alignment and stabilization is indicated whenever vertebral instability is suspected clinically or when it is documented by dynamic imaging. The most common neurological conditions requiring stabilization in the thoracolumbar region are vertebral fractures and luxations. Surgical treatment of vertebral fracture/luxation includes vertebral realignment, decompression and stabilization. Occasionally, neoplastic and infectious diseases causing vertebral instability, malalignment or malarticulation (e.g. discospondylitis) may require surgical decompression, debulking and stabilization.

Degenerative and/or congenital disease in the thoracolumbar region, leading to stenosis of the vertebral canal (e.g. synovial cysts, congenital vertebral anomalies and scoliosis), is often treated by stabilization in conjunction with a decompressive laminectomy.

Vertebral pins/screws with PMMA and vertebral body bone plates provide the most rigid fixation in this region, and permit the most accurate anatomical alignment of the vertebral column.

**Complications:** Intraoperative complications usually result from poor visualization of spinal cord and nerve roots during implant placement and result in iatrogenic trauma to neural tissues. Iatrogenic vertebral fractures, implant migration and failure (Figure 21.9),



Lateral postoperative radiograph obtained from the patient in Figure 21.8. The dog had been neurologically normal since recovering from the surgery 5 years earlier. One of the four original pins, used to stabilize the thoracic spine, has migrated into the accessory lung lobe. Although it was not causing any clinical signs, the lung lobe was resected to prevent further migration and the remainder of the implant removed.

as well as infection, are less common postoperative complications.

#### Thoracolumbar disc fenestration

While debate surrounds the role of thoracolumbar disc fenestration, it is the authors' opinion that annular fenestration with nuclear pulpectomy of at-risk intervertebral discs (T11–L3) is indicated in chondrodystrophic breeds with degenerative disc disease.

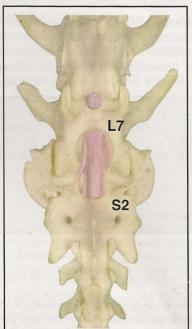
# Foramenotomy and/or pediculectomy

Enlargement of the intervertebral foramen may be done with or without removal of a portion of the pedicle. This provides access to masses within the intervertebral foramen and ventral aspect of the vertebral canal. This approach has the advantage of maintaining the integrity of the articular facets.

# Lumbosacral spinal surgery

#### **Dorsal laminectomy**

Compression of the cauda equina may result from: malarticulation/malformation; instability; vertebral canal stenosis, causing secondary degenerative joint disease; ligamentous hypertrophy; and/or disc degeneration at the lumbosacral junction. Excellent visualization of the cauda equina, L7-S1 dorsal annulus, articular processes and surrounding soft tissues is possible following dorsal laminectomy at the lumbosacral junction (Figure 21.10). The cauda equina may be retracted gently to visualize underlying structures, such as the dorsal annulus, as well as to assess the L7 nerve root as it enters the intervertebral foramen. Nerve roots of the cauda equina may be easily biopsied from this approach and extradural as well as intradural masses excised. Secondary compressive osteoarthritis. ligamentous hypertrophy and disc protrusion may be treated by decompressive dorsal laminectomy, with or without stabilization.



#### 21.10

Dorsal laminectomy at the lumbosacral junction. There is good visualization of the conus medullaris and nerve roots of the cauda equina. With gentle traction of these structures laterally, the dorsal annulus of the intervertebral disc can be seen and the L7–S1 intervertebral foramen palpated.

**Complications:** Complications associated with lumbosacral spinal surgery are uncommon.

- Intraoperative haemorrhage around nerve roots and iatrogenic trauma to nerve roots can cause pain and worsening of lower motor neuron signs (to the tail, bladder, anal sphincter and sciatic nerve).
- Seroma formation at the surgical site can occur, especially in animals not strictly confined in the immediate postoperative period.
- Extensive removal of articular facets and pedicles may encourage the formation of a clinically significant laminectomy membrane, although this is not often seen until weeks or months following surgery.
- Discectomy done in conjunction with dorsal decompression may predispose the patient to discospondylitis and/or instability at the lumbosacral junction (Figure 21.11).





(a) Lateral myelogram of the LS region of a 3-21.11 year-old Staffordshire Bull Terrier 6 weeks after a dorsal decompressive laminectomy at L7-S1. The dog was in severe pain. There is marked truncation of the conus medullaris (arrowed) and questionable lysis and sclerosis of L7-S1 vertebral endplates. The clinical signs resolved following reoperation and removal of a compressive laminectomy membrane. (b) Lateral radiograph of the LS region taken 6 weeks later following recurrence of clinical signs. There is marked lysis and sclerosis of the L7-S1 vertebral endplates consistent with discospondylitis (arrowed). The dog was placed on longterm, broad spectrum antibiotic therapy. Clinical signs improved immediately and radiographic signs improved over the course of several months.

## Foramenotomy/facetectomy

Entrapment of the L7 nerve root is a common occurrence in many conditions resulting in lumbosacral stenosis. Foramenotomy in conjunction with dorsal laminectomy may be done to relieve compression of nerve roots and associated apparent pain and/or dysfunction. Complete facetectomy is rarely indicated.

#### Lumbosacral stabilization

Lumbosacral stabilization is controversial. Indications for stabilization of the lumbosacral joint have not been agreed upon uniformly. In general, stabilization of the joint may be indicated when there is strong evidence of excessive movement, based on dynamic imaging studies. Decisions are complicated by:

- Variations in normal and abnormal anatomy within and between breeds
- Variations in imaging techniques and positioning
- A paucity of biomechanical data relating to the lumbosacral joint.

Techniques using transarticular pins or screws have been described (Slocum and Devine, 1986); however, the authors' preferred technique for internal fixation of the lumbosacral joint uses PMMA and pins placed in the L7 and S1 vertebral bodies (Sharp, 2002). This is accomplished accurately following decompressive dorsal laminectomy. Pin/screw placement may cause fracture of L7-S1 facets during stabilization, as well as there being the potential for implant failure and migration.

# **Cranial surgery**

Thorough neurological assessment, along with a good understanding of underlying pathophysiological processes, is essential for effective medical and surgical decision-making. Neurosurgeons need to be familiar with intracranial anatomy and have experience interpreting neuroimaging studies. Standard anaesthetic and physiological monitoring equipment is used to monitor body temperature, heart rate and rhythm, blood pressure, blood gases, and urine production. Patients should ideally recover in an intensive care unit where physiological monitoring is continued, and ICP monitoring, mechanical ventilation and blood products are available (see Chapter 20).

#### Indications

Intracranial surgery is most frequently performed to:

- Remove neoplastic masses
- Decompress and debride traumatized brain tissue
- Remove depressed skull fractures
- Biopsy intracranial lesions
- Stabilize elevated intracranial pressure (ICP).

Less commonly, surgery may be indicated for:

Drainage/evacuation of intracranial granulomas (fungal, foreign body) or abscesses (bacterial, fungal)

- Treatment of congenital anomalies (e.g. fenestration of intracranial intra-arachnoid cysts)
- Placement of ventriculoperitoneal shunts.

In the future, intracranial surgery may also be indicated for the treatment of refractory seizures.

# **Approaches**

Maximum exposure of a lesion is particularly important with intracranial surgery to avoid excessive brain manipulation that may predispose the patient to iatrogenic brain injury and associated complications. To this end, surgical approaches often consist of a combination of standard approaches (Figure 21.12).

Term	Definition	
Craniotomy	Any operation on or incision into the cranium	
Craniectomy	Removal of a part of the cranium	
Rostrotentorial craniotomy	Removal of the parietal/occipital bones to expose the frontal, parietal, occipital and temporal lobes of the brain	
Caudal fossa craniotomy	Removal of the caudal portion of the occipital bone and underlying osseous tentorium cerebelli with occlusion of the transverse sinus to allow access to the cerebellopontine angle and caudal occipital lobe	
Transfrontal craniotomy	Entry into the cranial vault by removal of the frontal bones overlying the frontal sinus as well as the inner bony table to allow access to the olfactory bulb and frontal lobe	
Suboccipital craniotomy	Entry into the caudal aspect of the occipital bones to allow access to the caudal cerebellum/brainstem.	

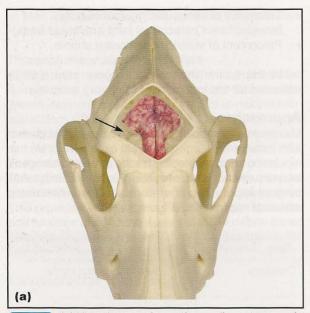
21.12 Terms commonly used in cranial surgery.

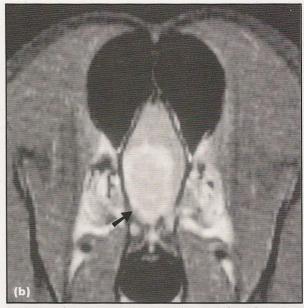
## Transfrontal craniotomy

Lesions involving the olfactory bulbs and rostrolateral portion of the frontal lobes of the brain are best approached through a bilateral transfrontal craniotomy/ craniectomy (Kostolich and Dulisch, 1987; Glass et al., 2000). Olfactory bulb/frontal neoplasms, abscesses or granulomas secondary to foreign body migration (Figure 21.13), fungal granulomas and nasal tumours invading through the cribriform plate are the most common conditions for which this approach is indicated.

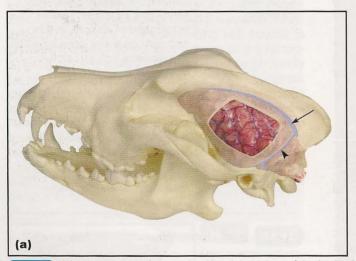
#### Rostrotentorial craniotomy

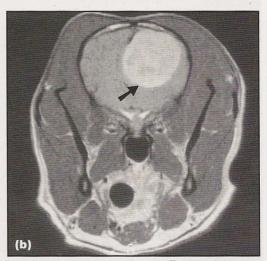
Lesions involving the lateral aspect of the parietal, temporal and occipital lobes of the cerebrum may be exposed by a rostrotentorial approach (Oliver, 1968; Niebauer et al., 1991) (Figure 21.14). The most common clinical indications are: resection/debulking of cerebral convexity or intraparenchymal masses; and craniectomy for stabilization of elevated intracranial pressure (ICP).





(a) Visualization of the olfactory/frontal lobes of the brain via transfrontal craniotomy. The large air-filled frontal sinus lies between the frontal bone and the inner table of the cranial vault (arrowed). (b) A transverse, post-contrast T1-weighted image of a 4-year-old male castrated Labrador Retriever with a contrast-enhancing olfactory bulb mass (arrowed). The mass, removed via transfrontal craniotomy, was a migrating foxtail that had presumably entered the cranial vault through the cribriform plate.





(a) Visualization of the parietal/occipital lobes of the brain via unilateral rostrotentoral craniotomy. The caudal extent of the craniotomy is limited by the transverse sinus (arrowhead) that receives venous blood from the dorsal sagittal sinus (arrowed). (b) A transverse, post-contrast T1-weighted MR image of a 10-year-old male castrated Shetland Sheepdog with a contrast-enhancing mass in the parietal lobe (arrowed). The tumour was removed by rostrotentorial craniectomy and was histologically identified as a meningioma. Note the marked shift of the falx to the right, caused by the mass.

The transverse sinus may be occluded unilaterally for more caudolateral exposure of the brain (Bagley *et al.*, 1997) (Figure 21.15). This allows access to the cerebellopontine angle, tentorial region and lateral aspect of the cerebellum. A bilateral rostrotentorial craniotomy/craniectomy also allows access to the dorsal aspects of the frontal, parietal and occipital lobes. However, complete occlusion of patent transverse sinuses bilaterally or of the dorsal sagittal sinus usually results in life-threatening circulatory compromise.

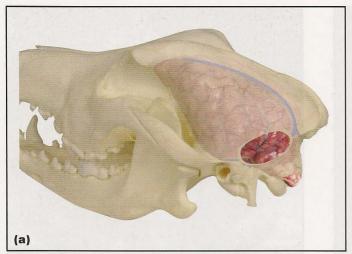
#### Suboccipital craniotomy

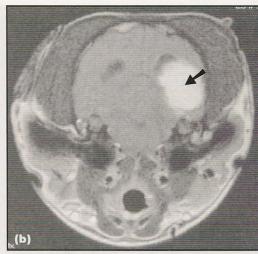
A suboccipital approach allows access to the caudal cerebellum, caudodorsal brainstem and craniodorsal

spinal cord (Oliver, 1968; Niebauer *et al.*, 1991) (Figure 21.16). Decompression and excision of mass lesions, and treatment of syringohydromyelia of the caudal brainstem/rostral cervical cord are accomplished via this approach.

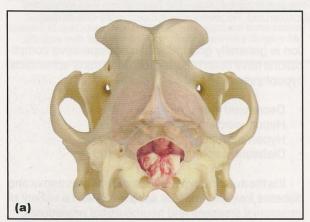
#### Other approaches

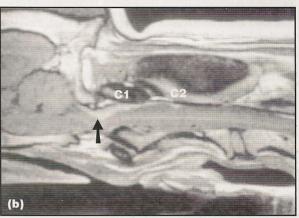
Access to the pituitary gland for resection of microadenomas is achieved by trans-sphenoidal hypophysectomy (Oliver, 1968; Meij *et al.*, 1998). Ventral approach to the caudal brainstem is possible; however, surgery is technically challenging and exposure is extremely limited (Oliver, 1968; Klopp *et al.*, 2000).





(a) Visualization of the caudolateral occipital lobe and cerebellum after occlusion of the transverse sinus. This approach is best used to treat mass lesions in the cerebellopontine angle, caudal occipital lobe and lateral cerebellum. It is often combined with unilateral rostrotentorial craniotomy. (b) Transverse post-contrast T1-weighted MR image of a mass lesion (arrowed) in the caudal occipital lobe appearing to arise from the tentorium. The lesion was amenable to resection via combined rostrotentorial and caudal fossa approaches.





(a) Visualization of the caudal cerebellum and rostral brainstem via suboccipital craniotomy. The location of the craniotomy is defined by the dorsal sagittal and transverse sinuses. (b) Sagittal post-contrast T1-weighted MR image of a mass lesion (arrowed) extending from the caudal brainstem to C2. Combined suboccipital craniectomy and dorsal cervical laminectomy allowed good visualization of the mass intraoperatively.

#### Complications

Incidence of perioperative complications associated with a poor long-term outcome from intracranial surgery involves many factors, including:

- Preoperative neurological status
- Location and size of mass
- · Histological diagnosis
- Concurrent medical disease
- · Age.

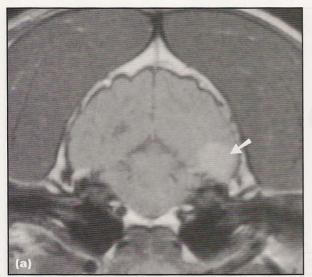
Patients should be assessed on an individual basis when surgery is contemplated. Serious common post-operative complications of craniotomy/craniectomy can be divided into neurological and non-neurological causes.

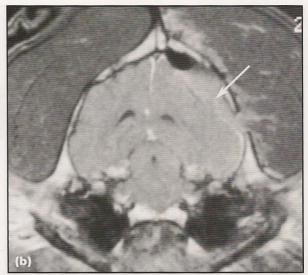
- Neurological complications generally result from iatrogenic injury to the brain.
- Non-neurological complications consist primarily of hypoventilation secondary to pneumonia or brainstem dysfunction.

# Neurological complications

latrogenic brain injury, leading to haemorrhage and/or cerebral oedema, ischaemia and progressive intracranial hypertension, is apparent immediately post-operatively and is reflected by deteriorating neurological status and possible brain herniation (Figure 21.17).

latrogenic intracranial infection is rare in dogs and cats and is usually not clinically apparent for at least 36-72 hours (Kostolich and Dulisch, 1987; Niebauer et al., 1991). Exposure of the brain to the frontal sinus following transfrontal craniotomy may increase the risk of postoperative infection, but clinical incidence is low. Infection is more likely to occur following reconstruction of large skull defects with prosthetic material such as PMMA (Bryant et al., 2003). Intraventricular pneumocephalus is a rarely reported complication following transfrontal craniotomy (Garosi et al., 2002). The risk of both infection and pneumocephalus may be reduced by closure of dural defects with fascial transplants or synthetic dura. Further short-term complications of transfrontal craniotomies include ipsilateral epistaxis and subcutaneous emphysema.





(a) Transverse T1-weighted image of a dog with a contrast-enhancing mass in the left caudal occipital lobe of the cerebrum (arrowed). The mass was resected via a caudal fossa approach with occlusion of the transverse sinus. (b) Six hours postoperatively MR images were obtained due to deteriorating neurological status. An extensive haematoma (arrowed) was diagnosed, involving the frontal, parietal and occipital lobes. The haematoma was evacuated via a rostrotentorial craniotomy and a bleeding meningeal vessel cauterized. Recovery was subsequently uneventful.

latrogenic generation of seizure foci following lesion resection, nervous tissue retraction or postoperative haemorrhage and scarring is a significant potential complication (Kostolich and Dulisch, 1987). Extensive craniectomy without reconstruction, particularly involving lateral/ dorsal approaches may result in compression of cortical tissue by overlying musculature. The incidence of long-term sequelae is unknown; however, cortical atrophy and acquired seizure disorders may occur (Figure 21.18).

The neurological status of many patients deteriorates immediately following surgery. This is often most evident following procedures involving the cerebellum and caudal brainstem, although long-term compensa-

Pathological section of the brain from a 5-yearold Springer Spaniel that had died after going into status epilepticus one year after decompressive craniectomy for progressive intracranial hypertension following a head injury. There is marked cortical atrophy and necrosis of the left cerebrum, presumably from the original head trauma; however, more recent cranial trauma to the unprotected cerebrum (where previous craniectomy had been done) could not be ruled out.

tion is generally good. Specific postoperative complications have been reported following trans-sphenoidal hypophysectomy and can include:

- · Decreased tear production
- Hypothyroidism
- Hypernatraemia
- Diabetes insipidus (Meij et al., 1998).

It is the authors' experience that hypernatraemia and diabetes insipidus may be associated with a variety of intracranial diseases and neurosurgical procedures.

#### Non-neurological complications

Aspiration pneumonia with secondary bacterial infection and/or chemical pneumonitis is the most common complication in craniotomy patients during the first 24–36 hours after the operation. The risk factors for aspiration appear to be multifactorial (Bagley *et al.*, 1997; Fransson *et al.*, 2001) and may include:

- Length of anaesthesia
- Regurgitation and vomiting
- Depressed pharyngeal/laryngeal function
- Seizures.

Fever and leucocytosis are the first signs seen, with radiographic changes occurring soon thereafter. Aggressive treatment including tracheal wash and culture, intravenous antibiotic therapy, oxygen therapy, nebulization and coupage and mechanical ventilation may be necessary.

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# Drug therapy for diseases of the central nervous system

Mark G. Papich

#### Introduction

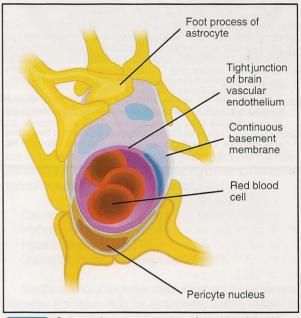
Drug therapy for diseases of the central nervous system (CNS) involves the complicating factors of drug penetration across the blood-brain barrier (BBB), the therapeutic effect on the CNS, and the potential for adverse effects. Drug efficacy for CNS disorders depends on the extent of penetration across the BBB after systemic administration. However, once a drug penetrates the BBB it may cause an undesirable effect unrelated to the drug's therapeutic effect. For example, antibiotics and antiparasitic drugs can produce adverse CNS effects that are not relevant to the drug's therapeutic action. This chapter will not review all aspects of CNS drug therapy or toxicity but will focus on important issues of drug penetration, antimicrobial therapy, anti-inflammatory therapy, anticancer therapy and adverse drug reactions. Readers are referred to specific chapters on anticonvulsant therapy (see Chapter 7) and treatment of traumatic CNS injury (see Chapter 19). For more in-depth information regarding toxicity, readers are encouraged to read the review article by Dorman (1995).

# **Drug entry to the brain**

For a drug to elicit an effect on the CNS, either the drug or a metabolite of the drug must penetrate the BBB. An exception to this is drug-induced vomiting. The area of the brain that stimulates vomiting, the chemoreceptor trigger zone (CRTZ), is in the brain's fourth ventricle, which is outside the BBB and thus exposed to circulating toxins and drugs.

#### Blood-brain barrier

There is free drug movement from the plasma into most tissues as fenestrations between capillary endothelial cells allow easy drug diffusion. However, the BBB is more restrictive; here, capillary endothelial cells have tight junctions and a continuous basement membrane (Johansson, 1990; Jolliet-Riant and Tillement, 1999) (Figure 22.1). In a recent review of 7000 drugs only 5% were able to affect the CNS (Pardridge, 2003). These drugs were primarily compounds used to treat depression, schizophrenia and insomnia. Most of these drugs were either of very small molecular weight or drugs with high lipophilicity that facilitated penetration across the BBB.



Schematic representation of the blood-brain barrier at the level of a cerebral capillary.

Drug penetration of the CNS may be possible via simple diffusion through endothelial cells or carriermediated transport (Pardridge, 1999). Small unbound lipid-soluble compounds can penetrate endothelial cells via simple diffusion. Passive diffusion correlates with the blood-brain drug concentration gradient and the lipid solubility of the drug, but is inversely correlated with the drug's extent of ionization and molecular weight (Jolliet-Riant and Tillement, 1999). In other words, if the drug has a large blood to brain concentration gradient, is lipophilic or non-ionized, it will tend to cross the BBB. For less lipophilic drugs, entry into the brain is possible if the concentration gradient between plasma and brain is high enough. Therefore, large doses or high plasma concentrations of drugs (e.g. penicillin antibiotics) can reach sufficient levels in the CNS to produce therapeutic or toxic effects. Carriermediated transport (CMT), which can occur via facilitated diffusion or active transport, allows carrier systems to transport glucose, fatty acids and other nutrients from the blood to the brain. The role of carrier-mediated diffusion for drug transport into the brain is minor except for a few basic drugs, such as antihistamines.

# Factors affecting drug entry into the brain

#### Ionization

Drug ionization affects the lipophilicity of a drug and its ability to enter the CNS. Only neutral (uncharged) drugs enter the CNS to a high enough extent to produce therapeutic or adverse effects. There are several examples of drugs for which the degree of ionization influences CNS effects. Of the antimuscarinic drugs the tertiary amines atropine and butylscopolamine can produce CNS changes, such as excitement. These drugs are uncharged and cross the BBB readily. Whereas, the quaternary amines have a charged nitrogen atom, which limits their ability to diffuse across the BBB. The quaternary amines, such as methylscopolamine, isopropamide, propantheline bromide and glycopyrronium bromide, are not associated with the same risk of CNS effects observed with tertiary amines.

#### Lipophilicity

Small lipophilic drugs cross the BBB more easily than larger or more hydrophilic drugs. Minor changes in structure can drastically change the drug's lipophilicity and ability to cross the BBB.

- Heroin, which has one additional hydroxyl group compared with morphine, crosses the BBB quickly after injection, producing a pronounced euphoric effect.
- In comparison, morphine has only one hydroxyl group and thus a slightly slower onset of effect.
- Diazepam has an additional methyl group compared with other benzodiazepines, which causes it to cross the BBB more rapidly and makes it the preferred drug for treating status epilepticus.
- Enrofloxacin appears to cross the BBB more easily than ciprofloxacin because the addition of an ethyl group makes it more lipophilic.

#### Molecular size

The molecular size of the drug affects penetration across the BBB. The molecular mass threshold for drugs active in the CNS appears to be <400–500 daltons. Most therapeutic drugs have a molecular weight below this threshold. In order to inhibit penetration across the BBB, drug molecules can be conjugated with larger molecules, such as proteins.

#### **Carrier-mediated transport**

Drugs can enter the brain via carrier-mediated transport (CMT). These transport systems carry nutrients to the brain from the blood. Such transport systems include the glucose transporter, the lactate transporter, the cationic amino acid transporter and the large amino acid transporter (LAT). An example of a drug that utilizes CMT is dopamine. Dopamine as the parent drug does not penetrate the BBB after systemic administration. However, when converted to an alpha-amino acid derivative, levodopa (L-dopa), it utilizes the LAT to be transported across the BBB. Once in the brain, levodopa is metabolized to dopamine where it is helpful for treatment of Parkinson's disease.

CMT can also transport anticonvulsant drugs. Gabapentin is a gamma-amino acid used to treat epilepsy. It mimics an alpha-amino acid and utilizes the LAT to penetrate the brain. It has been observed that gabapentin is effective in some patients who were refractory to other epileptic drugs. Perhaps an explanation is that if refractoriness to anticonvulsant drugs is mediated by over-expression of P-glycoprotein (see below) in some patients (Pedley and Hirano, 2003), a drug that utilizes another transport system may be more effective.

#### P-glycoprotein

A transmembrane protein coded by the multi-drug resistance (MDR) gene is present in the BBB to 'pump' drugs out of the CNS. This protein is called P-glycoprotein (P-gp) and has also been known as MDR1 and the ATP-binding cassette subfamily B member 1, or ABCB1. P-gp is also located in the gastrointestinal tract, placenta and kidneys, and other organs (Preiss, 1998). Thorough reviews have been presented recently to discuss the role of P-gp in the functional BBB (Demeule et al., 2002; Sun et al., 2003). P-gp is now regarded as an integral part of the functional BBB and an important determinant of drug penetration into the CNS. P-gp may exclude important drugs, such as dexamethasone, anti-viral (anti-HIV) drugs, anticancer drugs (used for treating brain tumours) and anticonvulsants. For example, it has been shown that resistance to anticonvulsant drugs may be related to polymorphism of the gene that codes for P-gp. In some clinical cases refractory to anticonvulsant drugs, the membrane pump is up-regulated, thus impairing drug penetration to an epileptogenic region of the brain (Pedley and Hirano, 2003).

P-gp participates in neuroprotection of the brain by regulating drug entry (Lechardeur et al., 1996) and acting as a 'guardian' of the CNS by preventing the accumulation of drugs in the brain (Demeule et al., 2002). Deficiency in BBB P-gp explains why some Collies and related breeds are susceptible to the rapeutic doses of ivermectin and similar drugs (discussed in more detail below). Inhibitors of P-gp that are of veterinary importance include ketoconazole, ciclosporin, calcium-channel blockers (diltiazem), erythromycin and antiarrhythmics (lidocaine and quinidine). Drug interactions caused by these inhibitors have allowed increased penetration of drugs that are normally excluded from the brain. For example, quinidine can increase the CNS effects of loperamide and of digoxin, which are ordinarily excluded from the brain (Sadeque et al., 2000; Lin, 2003).

# Differences between BBB and CSF transport

Some investigators have made the mistake of equating BBB transport to blood—CSF transport. It is not legitimate to evaluate drug brain penetration on the basis of penetration into the CSF. Drug entry into the CSF is not an index of BBB transport. Drugs that enter the CSF may be transported out quickly via absorption by the arachnoid villi. The endothelial cells of the brain represent a surface area of exchange that is 5000 times greater than the blood—CSF barrier. Therefore, the blood—CSF barrier is insignificant for determining drug penetration to the brain.

# **Antimicrobial drug therapy**

Activity and efficacy of antibiotics for treatment of CNS infections in small animals have not been critically evaluated. There are no documented clinical studies that have examined the efficacy of various antibiotics for CNS infections in veterinary patients and thus we continue to extrapolate data generated from human studies. Fortunately, primary bacterial infections of the CNS and meninges are uncommon in small animal medicine. However, bacterial infections of the CNS can arise as a complication from other primary diseases, such as otitis media (Spangler and Dewey, 2000) or nasal cavity infections, or due to contamination from surgery or other invasive techniques, such as epidural puncture. Other infectious agents, including fungi, protozoa, rickettsial agents and viruses may all infect the CNS. Therapeutic guidelines are developed from the experience of veterinary surgeons and extrapolated from experience in humans and laboratory animal studies.

This section of the chapter will focus on antibacterial, antifungal and antiprotozoal drugs. Antiviral drugs, although important in people, have never been examined for small animal nervous system infections, even though these infections do indeed occur (e.g. from tickborne disease or other sources) (Leschnik *et al.*, 2002; Yanai *et al.*, 2003). There are no published references to guide antiviral treatment of CNS infections in small animals, except for a few accounts of the use of aciclovir or famciclovir for treating herpesvirus and FIV dementia in cats.

#### **Antibacterial drugs**

With respect to treatment principles, an excellent review of treatment in humans was presented by Quagliarello and Scheld (1997). Meningitis in people is usually caused by Haemophilus influenzae, Streptoccus pneumoniae or Neisseria meningitidis. Enteric Gramnegative bacteria (e.g. Escherichia coli) may be opportunistic pathogens in severely immunocompromised patients or as a complication of neurosurgery. Reports of CNS infections are few in veterinary literature. The three most common bacterial pathogens in humans are not listed as CNS pathogens for small animals. When bacterial infections of the CNS occur in animals, it is anticipated that the most common organisms will include Streptococcus spp., Staphylococcus spp. and enteric Gram-negative bacilli, such as E. coli and Klebsiella pneumoniae. In a retrospective review of 23 cases of bacterial meningoencephalomyelitis in dogs, E. coli, Streptococcus and Klebsiella were the most common isolates (Radaelli and Platt, 2002). Unfortunately these bacteria were all identified from postmortem examination of nervous tissues (18 of 23 dogs). In only one of the 23 dogs was there a positive culture of the CSF ante-mortem. The study did not evaluate effectiveness of antibacterial treatments.

The BBB prevents many antibiotics accessing the CNS. This presents a problem with achieving adequate bactericidal drug concentrations in the CSF. Here, more than in other tissues, high bactericidal drug concentrations are needed because of the limited

natural bactericidal ability of the CNS. This deficiency of CNS defence mechanisms is attributed to the low protein content, low antibody levels and few phagocytic cells (Täuber *et al.*, 1984). Drugs that *do not* achieve adequate concentrations in the CNS include:

- Cephalosporins (except third generation)
- Penicillins
- Aminoglycosides.

For these drugs, high doses should be administered in order to produce an adequate concentration gradient between the systemic circulation and the brain to facilitate diffusion into the CNS. Antibiotics with better penetrability include the third generation cephalosporins, metronidazole, carbapenems and trimethoprim.

#### Cephalosporins

The third generation cephalosporins are the most active against Gram-negative bacteria, especially enteric organisms that are resistant to other cephalosporins. Cephalosporins are relatively polar antibiotics that are minimally lipid-soluble and have poor intracellular penetration. Ordinarily they have poor distribution to the CNS. However, third generation cephalosporins are exceptions and, among them, cefotaxime, ceftazidime, ceftizoxime and ceftriaxone achieve drug concentrations in the CSF that are considered bactericidal for most Gram-negative bacteria. Therefore, it is these drugs that should be the preferred drugs for treating serious bacterial infections of the CNS.

Cefotaxime is the preferred drug for small animals because it is highly active against Gram-negative enteric bacteria and Streptococcus spp. and it is the one that veterinary surgeons have the most experience with. Although there are no published studies which evaluate the use of cefotaxime in veterinary patients, clinicians have relied on some published pharmacokinetic studies (Guerrini et al., 1986; McElroy et al., 1986) to guide dosing. The pharmacokinetics between dogs and humans are similar enough that doses, as well as clinical uses, have been extrapolated from human medicine. Generally, cefotaxime is administered intravenously, intramusculary or subcutaneously to dogs and cats at a dose of 30 mg/kg every 8 hours. When administered subcutaneously to dogs and intramusculary to cats it was found that the absorption rates were high (Guerrini et al., 1986; McElroy et al., 1986) but that intramuscular and subcutaneous injections can cause pain.

Ceftazidime is most active in the treatment of *Pseudomonas* spp. against which all of the other cephalosporins, except cefoperazone, have little or no activity. Ceftazidime has been studied in dogs (Acred, 1983; Matsui *et al.*, 1984; Moore *et al.*, 2000); it has a short half-life (less than 1 hour) and volume of distribution similar to that in humans. Dosages have ranged from 20–30 mg/kg q12h for *Enterobacteriaceae*, to 30 mg/kg q4h for *Pseudomonas* (Moore *et al.*, 2000).

Ceftiofur has been used extensively in cattle and is now approved for use in horses and dogs. However, at the doses at which it is currently registered for dogs (2.2 mg/kg s.c. once daily) it is *not* expected to attain

concentrations in the CNS that are high enough to treat Gram-negative infections. Higher doses are not recommended because high doses of ceftiofur have caused bone marrow suppression in dogs.

There are three third generation cephalosporins that can be administered orally. Of these, two have been used in veterinary medicine, cefixime (Lavy *et al.*, 1995) and cefpodoxime proxetil. However, these are not used for treating CNS infections because it has not been shown that they achieve effective CNS levels.

#### Penicillins

Penicillins include penicillin G, ampicillin and amoxicillin. The penetration of these drugs into the CNS is poor. Except for sensitive *Streptococcus* spp. (that have low MIC values) these drugs should not be used for treating infections of the CNS. There are no published reports of successful use in small animals.

An exception is in the treatment of tetanus. The organism that causes tetanus (*Clostridium tetani*) is highly susceptible to penicillins. The organism elaborates a toxin (tetanospasmin) that produces excitation by binding to receptors in the CNS. When treating tetanus, drug penetration into the CNS is not necessary because it is a peripheral infection, even though the toxin produces CNS effects.

#### Carbapenems

The carbapenems include imipenem—cilastatin and meropenem. These drugs are the most active of any currently available antibiotics against a broad spectrum of bacteria. Imipenem has been associated with CNS adverse effects, including seizures, especially in human patients with meningitis. For this reason meropenem should be used instead when a highly active drug is needed, especially to treat infections that may be resistant to other drugs (Edwards and Betts, 2000). Small volumes can be administered subcutaneously with almost complete absorption. Based on pharmacokinetic experiments (Bidgood and Papich, 2002) the recommended dose for meropenem is 12 mg/kg s.c. q8h. For sensitive organisms in the urinary tract 8 mg/kg s.c. q12h can be used.

## Trimethoprim-sulphonamide

Sulphonamides have been used alone in veterinary medicine for many years. Combination products that contain trimethoprim are more effective for systemic use. Examples of available formulations include:

- Trimethoprim and sulfadiazine
- Trimethoprim and sulfamethoxazole.

Trimethoprim—sulphonamides are characterized by their good distribution to most tissues in the body. However, trimethoprim is more widely distributed than sulphonamides, especially to tissues such as the CNS.

Trimethoprim—sulphonamides have activity against both bacteria and protozoans. It is difficult to correlate plasma drug levels (and plasma elimination rates) with clinical efficacy and dosing intervals because trimethoprim persists longer in some tissues than in the

plasma. The optimum dosing regimen depends on the underlying disease. The recommended dose for CNS infections in dogs and cats is 15–30 mg/kg q12h.

#### Chloramphenicol

Chloramphenicol has been widely recommended for treatment of bacterial CNS infections. However, this drug is not as readily available as it used to be. Its activity against Gram-negative bacteria and its distribution into the CNS are not adequate to treat most infections as it does not reach bactericidal concentrations (Rahal and Simberkoff, 1979; Cherubin *et al.*, 1984).

#### Metronidazole

Metronidazole is indicated for treatment of CNS infections caused by anaerobic bacteria, particularly Bacteroides fragilis or its relatives. Metronidazole is lipophilic and penetrates the CNS. Doses have varied but are in the range of 10-20 mg/kg orally q8h-12h. The dose in cats often is one-quarter of a 250 mg tablet per cat, which is equivalent to 62.5mg. The most significant adverse effect is neurotoxicity, which is obviously a drawback if metronidazole is selected for treating CNS infections. The reactions observed appear to be caused by inhibition of the gamma-aminobutyric acid (GABA) neurotransmitter. These effects appear to be dose related, but have been associated with moderate doses of 33-83 mg/kg/day (Evans et al., 2003) as well as high doses of 67-129 mg/kg/day (Dow et al., 1989). Metronidazole has caused ataxia, lethargy, paresis, proprioceptive deficits, nystagmus, tremors and seizure-like signs in dogs. Dogs recover if drug administration is discontinued but recovery may take 1-2 weeks (Dow et al., 1989). However, when diazepam was administered as a treatment (0.2-0.69 mg/kg i.v. or orally q8h for 3 days) recovery was faster (Evans et al., 2003).

#### Fluoroquinolones

Fluoroquinolones include enrofloxacin, marbofloxacin, difloxacin and orbifloxacin. All of these are approved for use in dogs in the UK and the USA; orbifloxacin, marbofloxacin and enrofloxacin are approved for cats. Despite the high volumes of distribution, and otherwise good tissue penetration, these drugs do not reach therapeutic concentrations in the CNS. There are no documented indications for using fluoroguinolones to treat CNS infections in animals (Papich and Riviere, 2001). In addition, one of the adverse effects is CNS toxicity. CNS side-effects (including seizures) have been associated with either high doses or intravenous doses given rapidly, leading to a warning on package inserts to use this class of drug with caution in animals with CNS disease. In clinical practice adverse CNS effects have been rare when these drugs are used according to label instructions.

# **Antifungal drugs**

Occasionally, fungal meningoencephalitis is identified in small animal patients (see Chapter 10). There are few studies to document efficacy of treatment for these infections. However, treatment options are available using drugs registered for human medicine, which can be extrapolated to animals.

#### Amphotericin B

Amphotericin B is a polyene macrolide antibiotic with antifungal activity. It has no effect on bacteria but is effective on some protozoans (e.g. *Leishmania*). It has been a valuable drug for the treatment of serious systemic fungal infections. However, it is tremendously toxic and requires careful administration and patient monitoring. Penetration of amphotericin B into the CNS is limited. Nevertheless, it has been used for the systemic treatment of cryptococcal meningitis and meningoencephalitis caused by other fungi, such as *Coccidioides immitis*, *Candida* and *Aspergillus*.

One of the most important drawbacks to amphotericin B treatment is toxicosis. The most severe adverse effect is nephrotoxicosis. Early reversible nephrotoxicosis is seen with each daily dose but permanent nephrotoxicosis is related to the total cumulative dose. Assessments of renal function should be carefully monitored throughout treatment. It may become necessary to abandon therapy with amphotericin if there is persistent azotaemia. Other adverse effects that may be observed include vomiting, tremors, pyrexia and anorexia. These effects may be associated with each daily treatment and are somewhat alleviated by premedication with antihistamine drugs and anti-emetics. Phlebitis is expected with intravenous administration; therefore, the sites for catheter administration are usually alternated.

Consult a reference on this topic before attempting to treat any patient with amphotericin B (Rubin, 1986). Nephrotoxicity is reduced if patients are pre-treated with fluid therapy (NaCl) and receive the infusion at a slow rate (over 4–6 h). A recommended dose of 0.25 mg/kg for the first treatment, then 0.5–1.0 mg/kg administered every other day until a total cumulative dose of 4–8 mg/kg has been given. The total cumulative dose is limited by nephrotoxicosis.

Subcutaneous administration: Malik et al. (1996) have reported on the subcutaneous administration of amphotericin B for cryptococcosis. In their report, amphotericin was administered to dogs and cats subcutaneously diluted in 0.45% saline and 2.5% dextrose at cumulative doses of 8–26 mg/kg. Except for local irritation, the injections were well tolerated and, unlike intravenous injections, higher doses were administered without producing azotaemia.

Intrathecal administration: Due to the poor penetration of amphotericin B across the BBB, intrathecal administration has been used. For this type of administration the conventional formulation of amphotericin B should be used. The intravenous formulation of 5 mg/ml may be further diluted to 0.25 mg/ml by mixing 1 ml of the solution (5 mg) with 19 ml of 5% dextrose solution. Typically the dose for the animal is diluted with CSF in the syringe. It is important to note that some dextrose solutions have a pH of <4.2 and the pH should be increased if necessary prior to intrathecal administration. For small animals a dose of 0.01–0.1 mg (total dose of base) should be administered every 48–72 hours. If the dose is tolerated it

may be increased to 0.25 mg. This is a risky procedure and should be performed only as a last resort.

**New formulations:** These new formulations are used in humans but have not gained widespread use in veterinary medicine due to their high cost. There are three of these formulations currently available (Plotnick, 2000):

- Amphotericin B lipid complex
- Amphotericin B cholesteryl sulphate complex
- Amphotericin B liposomal complex encapsulated in a lipid bilayer.

Amphotericin B lipid complex is a suspension of amphotericin B complexed with two phospholipids. This formulation has been the most extensively evaluated in dogs, it is the least expensive, and was shown in one study to be safe and effective in dogs at a cumulative dose of 8–12 mg/kg. Amphotericin B cholesteryl sulphate complex is a colloidal dispersion, also called ABCD (amphotericin B colloidal dispersion). The amphotericin B liposomal complex encapsulated in a lipid bilayer has been used successfully to treat a German Shepherd Dog with discospondylitis due to disseminated *Aspergillus* infection (personal communication, N Olby).

The advantage of these lipid and cholesteryl formulations of amphotericin B is that, in comparison with the conventional formulation of amphotericin B (amphotericin B deoxycholate), these can be given at higher doses to produce greater efficacy with less toxicity (Hiemenz and Walsh, 1996). Amphotericin B lipid complex is 8-10 times less nephrotoxic in dogs than the conventional formulation of amphotericin B. These lipid complex formulations of amphotericin B have been administered at a dose of 3 mg/kg or more, compared with 0.25-0.5 mg/kg of the conventional formulation (Walsh et al., 1999). Decreased toxicity is attributed to a selective transfer of the lipid complex amphotericin B, releasing the drug directly to the fungal cell membrane and sparing the mammalian cell membranes. Reduced drug concentrations in the kidneys and diminished release of inflammatory cytokines from the amphotericin B lipid complex compared with the conventional formulation may also prevent adverse reactions. Improved efficacy is attributed to the higher doses that can be administered, selective delivery of the drug to fungal cell membranes, and the concentration of the drug in inflammatory cells, which can deliver the drug directly to the site of infection.

# Azole antifungal drugs

The only two oral azole antifungal drugs that should be used for systemic treatment of meningitis or meningoencephalitis caused by fungi are itraconazole and fluconazole. Ketoconazole has poor penetration into the CNS and should not be used for this indication. Enilconazole (which also has been called imazalil) has been used to treat nasal aspergillosis in dogs. It is reported to have a vapour effect and, if instilled into the nasal cavity of dogs, will control fungal growth (Sharp et al., 1991). It has been used successfully

to treat sinonasal aspergillosis in dogs, therefore preventing more serious invasion into the CNS (Zonderland *et al.*, 2002).

Itraconazole: Itraconazole is one of the most popular of the azole drugs. It is usually used to treat systemic fungal infections or yeast infections, but also may be indicated to treat cryptococcal meningoencephalitis. It is highly lipophilic and attains high concentrations in tissues (Van Cauteren et al., 1987). Even though the concentrations in aqueous fluids, such as aqueous humour and CSF, are low (this drug is not watersoluble) the levels in the tissues are high enough for treatment of CNS infections (Denning et al., 1989). Although specific tissue concentration studies are not available for dogs or cats, itraconazole may attain high enough tissue concentrations for effectiveness against CNS fungi (Perfect et al., 1986).

In cats itraconazole has been used at a dose of 10 mg/kg q24h and has been well tolerated, although anorexia can occur as a side-effect. Liver injury is also possible, especially at high doses. In an evaluation of 35 cats with confirmed *Cryptocococcus neoformans* infection, cats were treated with itraconazole at a dose of either 50 mg/day or 100 mg/day (Medleau *et al.*, 1995). Adverse effects were observed in 26% of the cats, most of them in the high-dose group, and included increased liver enzymes, anorexia and weight loss. Successful outcome was observed in 57% of the cats (average dose 13.8 mg/kg/day) and improvement was observed in 29% of the cats. Median duration of treatment was 8.5 months.

Dosages used in dogs have been 2.5–5 mg/kg/day and as high as 5–10 mg/kg/day for the treatment of blastomycosis; 5 mg/kg/day is the most commonly recommended dose (Legendre, 1995) and may be as effective as high doses with less toxicity. Presumably, this dose would also be considered for CNS infections.

Adverse reactions are possible but most are dose-related. If adverse effects are observed (e.g. anorexia) the dose should be lowered. According to Legendre (1995) about 10% of dogs receiving the recommended doses of itraconazole develop hepatic toxicosis. Liver enzyme elevations may occur in 10–15% of dogs. Hepatic toxicosis is also possible in cats. Anorexia may occur as a complication of treatment, especially with high drug doses and high drug serum concentrations. Anorexia usually develops in the second month of therapy in dogs.

Itraconazole is available as 100 mg capsules. The granules in these capsules may be added to food for convenience. It is better absorbed with food and should not be administered with an antacid or acid-suppressing drug (e.g. famotidine, omeprazole) because high stomach pH will decrease absorption. It is also available as a 10 mg/ml cherry-flavoured oral liquid formulation (Willems et al., 2001). The oral solution formulation is a combination of the drug with cyclodextrins. Cyclodextrins are permeability enhancers made up of oligosaccharides with a hydrophilic outer surface and a lipophilic inner surface. They form complexes with very lipophilic drugs, such as itraconazole, allowing them to remain

soluble in solution. Since dissolution is the rate limiting step in the absorption of most orally administered drugs, the liquid formulation has a higher absorption rate and is less dependent on feeding than the capsule formulation. In a study in cats, itraconazole oral solution appeared to be much better absorbed than a capsule (Boothe *et al.*, 1997) even when cats were fed with each administration of the capsule. The long half-life of itraconazole in the cats of this study supports once-daily dosing.

Fluconazole: Fluconazole has been used more commonly than itraconazole for treatment of fungal meningoencephalitis. It has been shown to attain effective drug concentrations in the CSF, although this should not necessarily be interpreted as being equivalent to concentrations in CNS tissues. The spectrum of activity is similar to that of other azoles, except that it has poor activity against Aspergillus. It has been the most commonly used oral drug for cryptococcal meningitis. Fluconazole has no effect on endocrine activity and has less tendency than itraconazole to cause drug interactions.

Fluconazole has different solubility characteristics to both ketoconazole and itraconazole and is absorbed well, regardless of other factors (such as feeding). It is available in tablets, oral suspension or as an intravenous injection. Fluconazole tablets and an oral suspension of 10 mg/ml are absorbed well; the oral dose is similar to the intravenous dose. Fluconazole is more water-soluble than itraconazole. Itraconazole does not dissolve in aqueous solutions and therefore fluconazole attains higher CSF concentrations than ketoconazole or itraconazole. Some clinicians have used this evidence to indicate that fluconazole is preferred for treating mycotic meningitis but superior efficacy of fluconazole over itraconazole has not been established clinically or experimentally (Perfect et al., 1986).

Fluconazole has a long half-life (25 hours) in cats with good absorption and distribution to the CSF and aqueous humour (Vaden et al., 1997). In humans the half-life is about 30 hours. For cats with systemic cryptococcosis, clinical studies have shown a benefit from a dose of 100 mg/cat/day in one or two divided doses. Other reported doses are 2.5-5 mg/kg q24h (Hill et al., 1995). Pharmacokinetic studies support a dose of 50 mg/cat per day (Vaden et al., 1997). Malik et al. (1992) treated 29 cats with cryptococcosis. The average dose of fluconazole was 50 mg/cat orally q12h and cats were treated for 2-6.5 months. Fluconazole was well tolerated, except for some anorexia, and all but one cat had clinical resolution. In dogs the dose is 10-12 mg/kg/day orally. However, in one case report (Tiches et al., 1998) a dog treated for CNS cryptococcosis developed adverse effects at a dose of 9.1 mg/kg/day and the dose had to be lowered.

# **Antiprotozoal drugs**

#### Pyrimethamine

Pyrimethamine is a diaminopyrimidine that is structurally related to trimethoprim, and acts via a similar

mechanism. The major difference is that pyrimethamine is more potent than trimethoprim in terms of inhibition of the dihydrofolate reductase enzyme of protozoans and therefore has been used to treat protozoal infections in people, horses, dogs and cats.

Pyrimethamine is often administered in combination with a sulphonamide for treatment of protozoal infections as the drugs act synergistically. In dogs this combination has been used to treat *Neospora caninum* infection and in cats it has been used for treatment of *Toxoplasma gondii*, although efficacy has not been established in cats. The formulations available are:

- Pyrimethamine 25 mg tablet
- Pyrimethamine 25 mg with sulfadoxine 500 mg.

Pyrimethamine is well absorbed after oral administration. The dose used for cats (to treat toxoplasmosis) is 1 mg/kg q24h plus sulfadiazine at a rate of 25 mg/kg orally q12h (for 14–28 days). The pyrimethamine dose for dogs is 1 mg/kg q24h plus sulfadiazine at a rate of 12.5 mg/kg q12h (for 14–21 days).

Adverse effects from pyrimethamine administration have included signs of folate deficiency, i.e. agranulocytosis, anaemia and thrombocytopenia. Although many veterinary surgeons provide oral folic acid or folinic acid supplements during treatment to prevent adverse effects associated with folate deficiency, effectiveness of this supplementation has never been established (Castles *et al.*, 1971). It is advised to monitor patients (e.g. complete blood count (CBC) periodically) for signs of folate deficiency during treatment.

#### Clindamycin

Clindamycin in high doses has been used to treat toxoplasmosis in dogs and cats. Clindamycin has in vitro activity against Toxoplasma gondii but clinical results of efficacy for treating toxoplasmosis are conflicting. The effective doses used are higher than those administered for bacterial infections. Appropriate doses are 12-25 mg/kg orally g12h (Dubey and Yeary, 1977; Greene et al., 1985; Lappin et al., 1989). Treatment duration is typically 2 weeks. At these doses adverse effects of diarrhoea, vomiting and reduced appetite are possible (Greene et al., 1992). In addition, the efficacy of clindamycin at these doses has been questioned. It may not be effective to clear organisms from the CNS of chronically infected animals (Greene et al., 1985; Lappin et al., 1989). Some studies of efficacy have only evaluated acute infections. In addition, clindamycin may not be effective for ocular forms of the disease (Lappin et al., 1992; Davidson et al., 1996). In human medicine clindamycin has been combined with pyrimethamine for treatment of toxoplasmosis. The effect of this combination has not been evaluated in dogs or cats.

#### Other antiprotozoal drugs

Trimethoprim-sulphonamides, discussed above, are sometimes used to treat protozoal infections.

# **Anti-inflammatory therapy**

Anti-inflammatory therapy is indicated for CNS infection and as an adjunct treatment of vasogenic oedema in diseases such as neoplasia. Corticosteroids are the most valuable anti-inflammatory drugs for CNS disease. Their anti-inflammatory properties have been reviewed elsewhere (Franklin, 1984; Papich and Davis, 1989; Barnes and Adcock, 1993). They reduce CNS oedema via their action on blood vessels, and they produce antiinflammatory effects via their action on neutrophils and inhibition of cytokine synthesis. For acute indications the drugs used should be rapid-acting and formulated for intravenous administration. The forms most often used are dexamethasone sodium phosphate, prednisolone (prednisone) sodium succinate and methylprednisolone sodium succinate (MPSS). These formulations have substitutions on the 17-alpha carbon (e.g. sodium succinate, sodium phosphate) to make them soluble in aqueous solutions. They can be administered with intravenous fluids or given intravenously at high doses. For more chronic therapy, oral treatments of prednisolone and dexamethasone have been used.

#### Corticosteroid use in CNS infections

In the treatment of CNS infection, cellular debris (particularly bacterial cell wall material) is liberated owing to the bactericidal effect of the antibiotics. Bacteriolysis promotes a cascade of inflammatory events releasing tumour necrosis factor-alpha, interleukins (IL-1, IL-6) and other cytokines. These mediators damage the CNS tissues, cause oedema and promote a further, more serious, inflammatory cascade. Similar inflammatory reactions are seen when treating fungal infections. In addition to bactericidal or fungicidal drugs, anti-inflammatory drugs should be employed as early as possible in the course of therapy when treating bacterial or fungal meningoencephalomyelitis.

The most common corticosteroid used during treatment of bacterial CNS infections in humans has been dexamethasone, although no comparisons have been made with prednisolone. Dexamethasone administered early in the treatment of bacterial meningitis decreases the inflammatory response associated with release of bacterial cell material (DeGans and van de Beek, 2002; Tunkel and Scheld, 2002; Lutsar et al., 2003). Dexamethasone should be instituted early in therapy; if treatment is delayed, benefits diminish. The dose most often recommended is 0.15 mg/kg of dexamethasone sodium phosphate (approximate antiinflammatory equivalent is 1 mg/kg of prednisolone), administered intravenously every 6 hours for 2-4 days. Because bacterial meningoencephalitis is rare in small animals, a definitive diagnosis should be reached prior to administering corticosteroids to patients with inflammatory CNS disease.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been considered alternatives to corticosteroids for anti-inflammatory treatment of the CNS. However, there is little published evidence either to support or to refute the use of these drugs for CNS disease. In one report, piroxicam was used as an adjunct to fluconazole when treating cryptococcal meningoencephalitis in

a dog (Tiches *et al.*, 1998). Neurological improvement was noted in the report but other drugs were also administered.

# Corticosteroid use in spinal trauma

Corticosteroids, specifically MPSS, have been administered to prevent further injury to the spinal cord caused by ischaemia and inflammation from trauma. The review by Olby (1999) provided an excellent summary of the studies in experimental animals that have evaluated the potential benefit of corticosteroids for this indication.

The action of corticosteroids was reviewed by Hall (1992) and by Brown and Hall (1992). The action of corticosteroids that appears to be most important for protection of spinal cord tissue from injury following trauma is that of inhibition of lipid peroxidation of membranes caused by oxygen-derived free radicals (Brown and Hall, 1992; Hall, 1992). This action is unrelated to the hormone effects of these drugs. High doses of MPSS (30 mg/kg) are required. (See Chapter 19 for full details of recommended dosing protocols for MPSS in spinal cord injury.) These doses far exceed the dose necessary to produce a typical corticosteroid effect from binding to glucocorticosteroid cellular receptors.

Lower doses are not effective for treating spinal cord trauma, even though at those doses all the corticosteroid receptors are probably occupied. A secondary beneficial effect may occur through the ability of corticosteroids to inhibit synthesis of inflammatory cytokines and suppress generation of arachidonic acid products (vasoactive prostaglandins), which may cause ischaemia of the neural tissue. MPSS is not as effective if treatment is delayed for more than 8 hours, and may actually be harmful. Administration of high doses of MPSS has been associated with side-effects (see Corticosteroid use for immunosuppression); therefore, its use is not recommended unless the animal has complete loss of voluntary motor function, as paretic animals have a good prognosis.

MPSS is a hemisuccinate ester, which is converted to a sodium salt to make it more water-soluble. Hydrocortisone is much less active, or in fact ineffective, even at doses of 120 mg/kg (Hall, 1985). The 1,2 double bond of prednisolone (which is lacking in hydrocortisone) appears to be a requirement for the anti-lipid peroxidation effect.

Current recommendations support the use of MPSS as the superior corticosteroid for spinal cord trauma rather than prednisolone or dexamethasone. The available evidence has established that dexamethasone is not as effective as methylprednisolone for preventing lipid peroxidation (Hoerlein *et al.*, 1985). It is likely that in order to achieve a high enough concentration in spinal tissue much higher doses of dexamethasone than used in experimental studies would be needed, which would increase the risk of adverse effects.

#### Corticosteroid use for immunosuppression

Corticosteroids (glucocorticoids) are usually the primary drugs used to treat or manage immune-mediated disorders of the CNS, including corticosteroid-responsive meningitis and corticosteroid-responsive meningomyelitis (Tipold, 2000). This disease is characterized

by inflammation of the CNS, without evidence of infection. Clinical features and other aspects of management of corticosteroid-responsive meningitis and corticosteroid-responsive meningomyelitis are discussed elsewhere in this book (see Chapter 13).

During immunosuppressive therapy, glucocorticoids exert their action by binding to intracellular receptors, translocating to the nucleus and binding to receptor sites that regulate gene expression (for example, expression of cytokines and immune function) (Boumpas et al., 1993). Glucocorticoids decrease neutrophil migration and egress into inflammatory tissue. This effect is attributed to suppressed expression of adhesion molecules, decreased adherence of granulocytes to the vessel endothelium and decreased diapedesis from the vessels. As a result, there is decreased movement of polymorphonuclear cells (PMNs) into the tissues in response to chemotactic stimuli. Glucocorticoids inhibit the normal functions of macrophages, including phagocytosis, inhibit the release of inflammatory cytokines from macrophages (e.g. IL-1, TNF-α and prostaglandins) and decrease expression of cytokines from lymphocytes (e.g. IL-2).

As reviewed by Cohn (1991), corticosteroids suppress the ability of macrophages to engulf cells and process antigens that are necessary to stimulate an immune response. Corticosteroids also profoundly affect lymphocytes. A complex series of interactions between antigens, macrophages, T cells and cytokines is important for immunological expression. Glucocorticoids suppress the activity of macrophages and the synthesis of IL-2. Glucocorticosteroids appear to have the most effect on T lymphocytes. Therefore, effects can be seen from suppression of helper cells to cellmediated immunity. Direct effects on antibody synthesis are not affected. In clinical veterinary medicine this action of glucocorticoids is dose-dependent. The lowest doses (using prednisolone as an example) produce physiological effects (0.25 mg/kg/day); higher doses produce anti-inflammatory effects (1.0 mg/kg/day); and still higher doses are considered immunosuppressive (for dogs 2-4 mg/kg/day). High doses are used for immunosuppressive therapy of the CNS.

#### Clinical use

For immune-mediated disorders, dosages of corticosteroids are higher than are necessary for anti-inflammatory therapy (by at least 2 times). These doses are usually administered initially on an everyday basis, and after remission of clinical signs every-other-day administration is often employed. There is no evidence from a well controlled study in animals to show that one glucocorticoid is superior to another when comparing efficacy. Nor is there any documentation to show that injectable therapy is more effective than oral treatment. For long-term therapy, intermediate-acting steroids (i.e. prednisolone) are used to avoid adverse effects, but dexamethasone is often used for acute treatment because it can be injected as a solution (e.g. dexamethasone solution).

Initial (induction) dosage regimens employed are in the range of daily doses of 2.2–4.4 mg/kg (prednisolone). A commonly cited immunosuppressive dose

of prednisolone for dogs is 2 mg/kg orally g12h. During the initial induction period the daily dose can be divided into a twice-daily dose to lessen (but not eliminate) some of the acute effects, such as gastrointestinal problems or behavioural changes. After the induction treatment phase the dose interval can be extended to once daily for another period of time until it is determined that the animal's disease is stable. If this is possible, the long-term maintenance dose should be 0.5-1 mg/kg every other day. The optimal dose that balances adverse effects and clinical response should be determined by titration. Immune-mediated diseases can vary greatly with respect to the level of glucocorticoids necessary to control clinical signs. Maintenance doses of 0.5-1 mg/kg q48h are possible in some patients but higher doses or the addition of other drugs may be necessary in others. Cats often require higher dosages, sometimes twice as much as dogs.

#### Adverse reactions from corticosteroids

The two adverse effects most likely to occur in humans from administration of corticosteroids (used to treat CNS trauma) are secondary infection (e.g. pneumonia) and gastrointestinal injury. An additional effect that may be important is that the hyperglycaemic action of corticosteroids may increase glucose concentrations in the CNS with secondary increases in lactic acid resulting in CNS injury. The clinical relevance of this latter effect in veterinary patients has not been established.

The gastrointestinal complications are the most serious consequence in animals (Toombs et al., 1980; Moore and Withrow, 1982; Hanson et al., 1997; Culbert et al., 1998; Rohrer et al., 1999a). The adverse effects associated with high doses of corticosteroids include vomiting, gastrointestinal bleeding, ulcers, perforating ulcers and diarrhoea. The proposed mechanisms involved in gastrointestinal injury from corticosteroids were reviewed by Toombs et al. (1986) and also discussed in the papers by Neiger et al. (2000) and Rohrer et al. (1999a). The adverse effects of corticosteroids are a result of a complex relationship between sympatheticparasympathetic imbalance, increased gastric acid secretion, stress, decreased synthesis of mucosal protective mechanisms and gastrointestinal ischaemia. Although these complications can be serious, most can be managed clinically by experienced veterinary surgeons. Despite their widespread use, neither omeprazole, misoprostol, gastric protectants (sucralfate) nor H<sub>2</sub>receptor blockers (cimetidine, ranitidine, famotidine) appear to prevent gastrointestinal problems associated with corticosteroids when they are used in surgery or to treat CNS trauma in dogs (Hanson et al., 1997; Rohrer et al., 1999b; Neiger et al., 2000). This suggests that neither increased acid secretion nor inhibition of prostaglandin synthesis plays an important role in gastrointestinal injury from corticosteroids.

# Other immunosuppressive drugs

Occasionally some anticancer agents, such as methotrexate, cyclophosphamide and cytarabine, are used for their immunosuppressive effects. The only other drugs used for immunosuppressive therapy of the CNS have been azathioprine and mycophenolate.

#### Mycophenolate

Mycophenolate is metabolized to the active compound mycophenolic acid (MPA). T and B lymphocytes are critically dependent on *de novo* synthesis of purine nucleotides and MPA is a potent inhibitor of inosine monophosphate dehydrogenate (IMPDH), an enzyme important for *de novo* synthesis of purines in lymphocytes. Therefore, it effectively suppresses lymphocyte proliferation and decreases antibody synthesis by B cells.

Mycophenolate is usually used in combination with glucocorticoids and/or ciclosporin. There are only a few clinical studies that have reported the use of mycophenolate in veterinary medicine for treatment of immune-mediated diseases. There is one report of treatment of myasthenia in a dog (Dewey *et al.*, 2000) and some experience with treating skin diseases (Byrne and Morris, 2001).

According to pharmacokinetic studies with mycophenolate in dogs, the elimination rate was rapid (with the half-life less than 1 hour) suggesting that frequent dosing may be required for successful therapy (Dewey et al., 2001). Because of its short half-life in dogs, mycophenolate may not be useful as a first-line treatment but may be useful as adjunctive therapy in some animals. Suggested doses have been approximately 10–20 mg/kg q12h. Adverse effects include nausea, vomiting and diarrhoea, which appear dose-related. For treatment of a myasthenic dog, 20 mg/kg orally q12h was initially administered and the dose lowered to 10 mg/kg q12h after adverse gastrointestinal effects developed (Dewey et al., 2000).

#### **Thiopurines**

Thiopurines have been used as a first-line therapy or as an alternative to nitrogen mustard alkylating agents for the treatment of immune-mediated disease. The most common drug used for this purpose is azathioprine. It is metabolized in the liver to the active metabolite 6-mercaptopurine (6-MP). In vitro studies indicate that some metabolism may occur at target cells responsible for immune effects. Azathioprine interferes with the de novo synthesis of purine nucleotides that are important for lymphocyte proliferation. 6-MP inhibits T cell lymphocyte function and helper cell effects on antibody synthesis, with little direct effect on B cells. In humans it has been suggested that azathioprine is more effective for IgG-mediated disease, whereas cyclophosphamide is more effective for IgM-mediated disease. This theory has not been tested in veterinary patients.

Clinical use: In veterinary medicine, azathioprine has been used for immune-mediated anaemia, colitis, immune-mediated skin disease, acquired myasthenia gravis and other immune-mediated diseases. Azathioprine is available as 50 mg tablets. A dose of 2 mg/kg orally q24h can be given. Long-term therapy is administered at a dose of 0.5–1.0 mg/kg every other day with prednisolone administered on the alternate days. In veterinary medicine this lag-period is probably shorter than the 2–8 months recognized in humans, and therapeutic benefits have been observed after only 3–5 weeks.

Because cats may be at risk of bone marrow suppression from administration of azathioprine, current recommended doses are as low as 0.3 mg/kg q24h or q48h; however, dose regimens of 6.25 mg (1/8 tablet) or 1–2.2 mg/kg every other day have been documented (Caciolo *et al.*, 1984; Beale *et al.*, 1992; Helton-Rhodes, 1995). Careful monitoring of CBC is recommended during treatment.

Adverse effects: Bone marrow suppression is a concern in all animals. Leucopenia and thrombocytopenia can be serious and gastrointestinal toxicity and hepatotoxicity are also possible. Gastrointestinal effects, such as nausea and diarrhoea, may be only temporary and subside after several days of therapy. There has been association (though not well documented) between the administration of azathioprine plus prednisolone and the development of acute pancreatitis in dogs. It has been suggested that this effect is caused by azathioprine decreasing pancreatic secretion in animals.

Metabolism: After azathioprine is converted to 6-MP. it is further metabolized by three routes to other metabolites. One metabolic route is via xanthine oxidase to inactive metabolites. Allopurinol will decrease this route because it inhibits xanthine oxidase. Another metabolic route is via thiopurine methyltransferase (TPMT), which is responsible for the conversion of 6-MP to non-toxic 6-MP nucleotides. In humans there is a genetic polymorphism that determines high or low levels of TPMT. Humans with low TPMT activity are more responsive to therapy but have a high incidence of toxicity (myelosuppression); humans with high levels of TPMT activity have a low incidence of toxicity but lower drug efficacy (Lennard et al., 1989). Most of the human population has high TPMT activity but about 11% have low levels and are more prone to toxicity. In humans with low TPMT activity, the dose of azathioprine must be lowered.

It appears that in dogs TMPT levels are highly variable in the population (Kidd *et al.*, 2004). TPMT activity varied 9-fold in a population of 177 dogs (Kidd *et al.*, 2004). Another study with fewer dogs indicated that 90% of dogs showed normal TPMT activity and 10% had low levels (White *et al.*, 1998). Cats, as expected, have low TPMT activity due to adverse effects (Foster *et al.*, 2000). It is possible that variations in TPMT activity among animals could account for azathioprine drug toxicity but further evidence is needed to document this phenomenon. Animals that are treated with azathioprine should have their bone marrow function monitored during initial therapy to identify those that may have low TPMT activity so doses can be adjusted accordingly.

# Anticancer chemotherapy of the nervous system

Although CNS cancer is common in companion animals, treatment of CNS tumours with chemotherapy is unusual in veterinary medicine. There is little information on treatment outcomes because there are no controlled studies in which anticancer treatments

have been evaluated. Therapeutic protocols, such as those available for other forms of cancer (Kitchell and Dhaliwal, 1999), are not established for CNS tumours; there are just a few case reports and anecdotal experience. In a review paper on treatment of CNS tumours, only brief mention is made of specific anticancer drugs (Moore et al., 1996). Some reports of treating CNS tumours in animals make no mention of specific anticancer agents (Kraus and McDonnell, 1996). Much of the medical therapy of CNS tumours involves palliation to control secondary problems, such as seizures or inflammation. Most often, anticonvulsant drugs are used to control seizures (see Chapter 7) and anti-inflammatory drugs (corticosteroids) are used to control oedema and inflammation caused by the tumour. Corticosteroids have been discussed above.

One of the challenges of applying cancer chemotherapy to CNS tumours is that most of these drugs do not penetrate the BBB well enough to achieve effective concentrations in the tumour. For example, doxorubicin, a popular anticancer drug for lymphoma and other tumours, does not cross the BBB and is not useful for treating CNS cancer. Cisplatin, another important anticancer drug, is over 90% bound to plasma proteins and also does not cross the BBB. On the other hand, drugs that penetrate the BBB have a high potential for causing adverse neurological effects. There is an account of increased toxicity caused by anticancer chemotherapeutic agents in a dog because the dog had a MDR1 deletion mutation (deficiency in P-glycoprotein) that led to increased penetration across the BBB (Mealey et al., 2003).

Anticancer drugs have many important adverse effects that must be managed when treating patients. All anticancer drugs produce some degree of toxicity to the patient because, in order to kill cancer cells, some death of healthy cells must be accepted. Usually it is the most rapidly dividing cells in the body that are affected, such as the bone marrow, hair and gastrointestinal epithelium. Some drugs have additional toxicity that affects specific organs. For example, doxorubicin has cardiotoxic effects in dogs and cyclophosphamide can cause bladder injury. To minimize toxicity, combination drugs have been used, antiemetics administered and concurrent therapy with corticosteroids employed.

Many drugs are administered at doses based on body surface area (mg/m²) rather than bodyweight (mg/kg). This dosing scheme has been used because body surface area correlates better with physiological functions and metabolic rate than does dosing on a mg/kg basis. The concept of dosing according to a physiological function (e.g. metabolic rate) is called allometric scaling. (Assuming that physiological function is correlated linearly with bodyweight is called isometric scaling.)

Although it has been assumed that dosing anticancer drugs according to body surface area is more accurate and less toxic than dosing on a mg/kg basis, this has become controversial. Some studies in dogs suggest that this method may not be safer (Arrington *et al.*, 1994). When administration of anticancer agents to

dogs was done by calculating doses by body surface area instead of bodyweight (Price and Frazier, 1998a,b), more toxicity occurred in smaller dogs. Nevertheless, until better information becomes available the drugs discussed in this section are given at dose rates adjusted by body surface area.

#### Alkylating agents

The major alkylating agents are the nitrogen mustards and the nitrosoureas. These drugs covalently alkylate various cellular constituents. Most importantly for cancer treatment, alkylation occurs between the bases of DNA molecules of rapidly dividing cancer cells. This reaction cross-links the bases of DNA, causing cessation of DNA synthesis and cell death. The most significant effect is to bind and cross-link double-stranded DNA; therefore, these drugs are referred to as bifunctional alkylating agents. Bifunctional alkylating agents are more cytotoxic and produce fewer drug-induced tumours than monofunctional agents. Alkylation of the DNA molecule causes abnormal base pairing, misreading of the genetic code and excision of bases, which prevents DNA transcription and RNA synthesis.

These drugs are more active on growing cells in the cell cycle than on dormant cells. However, they can act at any point of the cell cycle and therefore are non-cycle-specific. They are most active when DNA is dividing, such as in the G1 Phase and S Phase. As a consequence, in addition to their effect on cancer cells, they will also affect rapidly growing normal cells such as bone marrow cells and gastrointestinal mucosa.

#### Nitrogen mustards

The nitrogen mustards (bischloroethylamines) are a group of bifunctional alkylating agents that alkylate various macromolecules, but preferentially alkylate N-7 of the guanine base of DNA. They are cytotoxic to cancer cells and are toxic to the rapidly dividing cells of the bone marrow.

Cyclophosphamide: Cyclophosphamide is probably the most potent of the nitrogen mustards. It is used in chemotherapy protocols for a variety of tumours: carcinomas; sarcomas; feline lymphoproliferative diseases; mast cell tumour; mammary carcinoma; and, especially, lymphoproliferative tumours (lymphoma). The main indication for the nervous system is treatment of CNS lymphoma and as an immunosuppressive agent in immune-mediated diseases. A typical dose is 50 mg/m² orally 4 days per week. Pulse doses may be as high as 200 mg/m² once a week to once every 21 days.

Cyclophosphamide must be metabolized to active metabolites for pharmacological effect and some of the activation requires a P-450 enzyme activation; other steps in the activation are non-enzymatic. The metabolites, hydroxyphosphamide and aldophosphamide, are cytotoxic. Aldophosphamide is converted at the tissue site to phosphoramide mustard and acrolein, which are responsible for its biological activity (i.e. alkylating activity and cytotoxicity). The half-life of the parent drug in dogs is 4–6.5 hours.

Toxic effects: In many protocols, cyclophosphamide is administered chronically at relatively low oral doses rather than large pulse doses. With low doses acute toxic effects are not as common. Nevertheless, with cyclophosphamide therapy, bone marrow suppression, gastrointestinal toxicosis and cystitis are important concerns. Cyclophosphamide is toxic to the bone marrow in a dose-dependent manner. After a large pulse dose, maximum toxicity occurs in 7–10 days but the effect is reversible because the stem cells are spared. Recovery usually occurs in 21–28 days. The nadir of bone marrow activity appears to be delayed in cats and it takes longer for the myelosuppression to resolve (Cotter, 1983).

Toxicosis to the gastrointestinal tract can occur because the cytotoxic products of metabolism affect the rapidly dividing cells of the gastrointestinal mucosa. Nausea and vomiting may occur as a consequence of acute therapy. Sterile haemorrhagic cystitis is a serious complication to therapy that may require abrupt termination of therapy. It is caused by the toxic effects of metabolites on the bladder epithelium (especially acrolein) that are concentrated and excreted in the urine

Various attempts have been made to decrease the injury to the bladder epithelium. Corticosteroids are usually administered with cyclophosphamide to induce polyuria and decrease inflammation of the bladder. The drug mesna (mercaptoethanesulfonate) provides free active thiol groups to bind metabolites of cyclophosphamide in the urine, decreasing haemorrhagic cystitis. Mesna is a thiol compound oxidized in the blood to a disulphide dimesna. It is taken up by kidneys and excreted in urine as mesna. In the urine, it combines with acrolein and forms inert non-toxic metabolites. This complex does not injure the epithelial cells of the bladder. The activity of mesna is limited to the urine and therefore it does not affect anti-tumour effect of cyclophosphamide. Cats are less susceptible than dogs to developing cystitis.

Another adverse effect is alopecia. This effect is reversible and is related to hair follicle toxicity. It is primarily seen in dogs with continuously growing hair (e.g. Poodles, Old English Sheepdogs). Cats do not tend to lose hair from cyclophosphamide treatment.

Immunosuppressive properties: Cyclophosphamide is frequently used for immune-mediated disorders in small animals. The effect of cyclophosphamide on these diseases is related to the cytotoxic effects on lymphocytes, including B cells. Mechanisms of immunosuppression include depletion of lymphocytes, suppression of B cell function, and suppression of cell-mediated immunity by T cells. Cyclophosphamide also suppresses neutrophil and macrophage function.

#### **Nitrosoureas**

The nitrosoureas have received the most attention for treating tumours of the brain, in particular gliomas. These drugs are more lipophilic and penetrate the BBB better than the other anticancer drugs. Two nitrosoureas are commonly used:

- Lomustine (1-(2-chloroethyl)-3-cyclohexyl-1chloroethylnitrosourea); known by the abbreviation CCNU
- Carmustine (1,3-bis-2-chloroethyl-1-nitrosourea);
   known by the abbreviation BCNU.

These drugs, in addition to being lipid-soluble, are alkylating agents. Both of the nitrosoureas are metabolized spontaneously to alkylating and carbamoylating compounds. The binding occurs preferentially at the O-6 of guanine. Bifunctional interstrand cross-links are responsible for the cytotoxicity of nitrosoureas. Oral absorption and high membrane penetration are attributed to high lipophilicity. Because oral absorption is high, these drugs can be administered effectively as tablets rather than an injection. After absorption, lomustine is metabolized to anti-tumour metabolites. Both the parent drug and the metabolites are lipid-soluble. The CNS penetration of lomustine has been estimated from the plasma:CSF ratio, which is 1:3.

Clinical use: Lomustine has been used more often than carmustine. It has been administered to small animals at doses of 70 mg/m² to 90 mg/m² orally every 4 weeks. For brain tumours, protocols of 60–80 mg/m² orally every 6–8 weeks have also been cited (Fulton and Steinberg, 1990). These protocols are quite different from those for humans, where a dose of as much as 150–200 mg/m² is recommended.

Adverse effects: The adverse effects of lomustine are primarily attributable to the bone marrow effects. In humans the time to nadir of bone marrow activity can be as long as 4–6 weeks, with slow recovery rates. In dogs maximal bone marrow effects are generally seen 6–7 days after dosing. The doses cited above have been used to minimize the bone marrow effects. At higher doses (e.g. 100 mg/m²) myelosuppression has been reported. Thrombocytopenia as a cumulative effect has also been reported from lomustine administration.

Nitrosoureas can be toxic to the rapidly dividing cells of mucosa. In humans, nitrosoureas have caused pulmonary fibrosis and hepatotoxicosis. In one report 6.1% of 179 treated dogs developed hepatotoxicity (Kristal et al., 2004). The doses administered were 50-110 mg/m<sup>2</sup>, at a minimum of every 3 weeks. Signs of hepatic injury were delayed for a median duration of 11 weeks and may be related to cumulative dose. The hepatic damage may be irreversible in dogs. In humans carmustine has been associated with a higher rate of hepatic injury than lomustine, but there are currently no reports of carmustine administration being used for treating tumours in dogs. In cats, lomustine has been used for treating tumours but there is no record of treatment for CNS tumours. Lomustine has been used at a dose of 50-60 mg/m<sup>2</sup> orally every 5-6 weeks. In cats maximum bone marrow toxicity occurs at 3-4 weeks.

# Cytarabine

Cytarabine is a compound isolated from a sea sponge. It has also been referred to as cytosine arabinoside and Ara-C. Cytarabine is metabolized to an active drug that inhibits DNA synthesis. It was once thought that its

action was via inhibition of the enzyme DNA polymerase, but the exact mechanism of action may not be known. The most common use of cytarabine is for the treatment of lymphoma and myelogenous leukaemia. Cytarabine is one of the drugs used in combination chemotherapy by veterinary surgeons (COAP protocols; see *BSAVA Manual of Canine and Feline Oncology, 2<sup>nd</sup> edition*). Cytarabine has been administered as a constant rate infusion, or as a slowly absorbed intramuscular or subcutaneous injection, because it has a short half-life (<20 minutes) when administered intravenously. Doses have been 100 mg/m² as a 48-hour infusion or 100 mg/m² s.c.

Although not lipophilic enough to cross the BBB after systemic administration, cytarabine has been used to treat CNS leukaemia and lymphoma because it enters the CNS tissues after the BBB has been disrupted by disease. Cytarabine has also been administered intrathecally for treatment of some CNS tumours. In a study of healthy dogs, after administration of 600 mg/m<sup>2</sup> i.v., the CSF:plasma concentration ratio was 0.62 ( $\pm$  0.14) (Scott-Moncrieff et al., 1991). It is not known how well the CSF drug concentration correlates with concentrations in brain tissue, but these levels may be high enough to treat some tumours of the CNS. The authors of this study acknowledge that this drug may be promising for treating tumours of the CNS in dogs but no reports of clinical use have been published to date.

Another use of cytarabine in dogs is as an alternative to corticosteroids for the treatment of granulomatous meningoencephalomyelitis. Cytarabine has been administered at a dose of 50 mg/m² s.c. twice daily for two days and repeated every 3 weeks (Nuhsbaum *et al.*, 2002). Cytarabine can markedly suppress bone marrow and can cause granulocytopenia, especially when administered as a continuous rate infusion. In addition it may cause nausea and vomiting.

#### Methotrexate

Methotrexate is considered an antimetabolite anticancer drug. It is primarily active in the 'S-Phase' of the cell cycle. Like other antimetabolites, methotrexate interferes with the biochemical reactions necessary for proper cell function, regulation or division. The structure of methotrexate is similar to that of folic acid. Subsequently, methotrexate binds and inhibits the dihydrofolate reductase enzyme (DHFR). The DHFR enzyme is a reducing enzyme necessary for purine synthesis. The reduced form of folic acid (tetrahydrofolate, FH4) acts as an important coenzyme for biochemical reactions, particularly DNA, RNA and protein synthesis. Methotrexate is used in some combination chemotherapy protocols, mostly for lymphoreticular neoplasia and osteosarcoma.

The action of methotrexate on CNS tumours is limited because, like other antimetabolites, methotrexate is most effective when tumour cells are in the logarithmic phase of growth. Many CNS tumours can be slow-growing. Penetration across the BBB is also a problem because folic acid analogues are polar molecules and cross the BBB poorly. In humans (data not available for dogs) the CSF drug concentrations are

only 3% of the corresponding plasma concentration. Intrathecal administration has been used in humans as a last resort. Another approach used in humans is the systemic administration of very high doses of methotrexate (>1.5 g/m²) with the intent of achieving high enough concentrations in the CNS to be effective. This can be compared with the usual doses given to dogs, of 2.5 mg/m² q48h or 0.5–0.8 mg/kg every 7–14 days. At the doses administered for CNS tumours in humans, systemic toxicity is high and rescue therapy with calcium folinate (leukovorin) must be used. Leukovorin is used because it is an antagonist of the action of methotrexate on the DHFR enzyme and therefore decreases the risk of toxicity.

In humans methotrexate also has been used as an immunosuppressive agent to treat diseases, such as rheumatoid arthritis, and as an abortifacient. Its major adverse effects in animals are anorexia, nausea, myelosuppression and vomiting.

# Glucocorticoids in cancer chemotherapy

Glucocorticoids are commonly used in cancer chemotherapy and are a component of some of the combination protocols. Prednisolone has been used as the sole drug for some tumours (e.g. mast cell tumours). Prednisolone is usually the drug of choice in anticancer protocols. A usual starting dosage is 40 mg/m² orally every day. When tumour remission occurs the dosage is frequently decreased to 20 mg/m² every other day.

Glucocorticoids are cytolytic for malignant lymphoid cells. The mechanism may be related to the synthesis of an endonuclease that disrupts DNA. Glucocorticoids have been used for the therapy of lymphoma as a single drug but tumour resistance develops rapidly. Glucocorticoids also decrease the inflammation associated with tumours and chemotherapy, and decrease the effects of TNF $\alpha$  (Beutler and Cerami, 1987). As discussed previously, because glucocorticoids cross the BBB they are effective for reducing the oedema and inflammation associated with some CNS tumours.

# Adverse CNS reactions caused by drugs

# Ivermectin and related drugs

The adverse CNS effects caused by ivermectin, and similarly acting drugs such as moxidectin and milbemycin, are well documented in the veterinary literature (Lovell, 1990; Dorman, 1995). The avermectin and milbemycin classes of parasiticides enhance the effects of GABA and stimulate its release from nerve endings. In parasites, increased GABA activity causes paralysis and death of the organism. Ordinarily dogs and cats are resistant to these effects because these drugs do not cross the BBB. However, when these drugs are administered to certain breeds of dog that permit them to cross the BBB, CNS toxicity results. Collies, Shetland Sheepdogs, English Sheepdogs, Australian Shepherd Dogs and perhaps other breeds have this susceptibility. It is now recognized that dogs susceptible to ivermectin toxicosis have a mutation in the

MDR1 gene that codes for P-gp in the BBB (Mealey et al., 2001, 2002; Nelson et al., 2003; Roulet et al., 2003). The adverse CNS effects of ivermectin are most likely caused by accumulation of the drug in the brain because P-gp, which normally would transport the drug out of the brain through the BBB, is deficient or inhibited. In mice deficient in expression of P-gp (CF-1 mice) the doses of ivermectin necessary to produce CNS toxicity are 100 times lower than doses that produce toxicity in other strains of mice (Lankas et al., 1997).

Approximately 30-50% of Collies are susceptible. Single doses of ivermectin >1000 μg/kg have been administered to other canine breeds but doses of 100-500 µg/kg administered to susceptible Collies have produced toxicity. Intoxication in dogs and cats has also been the result of administering concentrated equine or bovine formulations at excessively high doses, or even following consumption of equine faeces. Most reactions have been observed with ivermectin because it has been available for the longest time. However, reactions to other related drugs moxidectin and milbemycin also have been reported in dogs (Tranquilli et al., 1991; Beal et al., 1999). Toxic effects from milbemycin at 20 times the recommended dose were shorter in duration than signs caused by ivermectin at 20 times the recommended dose (Tranquilli et al., 1991).

Clinical signs in affected dogs include incoordination, ataxia, mydriasis, tremors, depression, behavioural changes, seizures (rare), blindness, coma and even death (Lovell, 1990). Reduced or absent cranial nerve reflexes have also been reported. In some dogs that have recovered, permanent behavioural changes have persisted. Many animals recover with supportive treatment but recovery may take up to 10 days or longer (60 days in one account) depending on the dose administered. There is no effective antidote for ivermectin-induced CNS adverse effects. Physostigmine, a cholinesterase inhibitor, has been used to alleviate some signs but it must be administered frequently (e.g. every 60-90 minutes) and is not recommended for routine treatment. Picrotoxin, a GABA antagonist, has also been used in isolated cases for treatment but is not recommended routinely because it can cause seizures.

# Other substrates for P-glycoprotein

The consequences of a deletion mutation in the *MDR1* gene that codes for P-gp may extend to other groups of drugs. The antidiarrhoeal drug loperamide ordinarily does not cause CNS effects after oral administration because it does not cross the BBB (Sadeque *et al.*, 2000). However, it has been reported that Collies are at a higher risk of CNS toxicity from loperamide (Hugnet *et al.*, 1996; Sartor *et al.*, 2004). An *MDR1* deletion mutation in a Collie was associated with toxicity from loperamide. Signs of toxicity included lethargy, rear limb weakness, disorientation and ataxia.

*MDR1* mutations or inhibition of BBB P-gp can potentially lead to CNS toxicity from other drugs. Toxicity caused by anticancer chemotherapeutic agents in a dog was attributed to an *MDR1* deletion mutation that led to increased penetration across the BBB (Mealey *et al.*, 2003).

#### **Antihistamines**

There may be several factors that determine the adverse effects of antihistamines on the CNS. First generation antihistamines cause sedation and behavioural changes as unwanted side-effects. First generation drugs include chlorpheniramine, diphenhydramine, clemastine and hydroxyzine. Some of the tricyclic antidepressant drugs, such as doxepin, produce some sedative effects through antihistamine action. The second generation antihistamines are not associated with these effects, which explains their popularity in human medicine (Papich, 1999). Such second generation drugs include terfenadine, fexofenadine, astemizole, loratadine and cetirizine. Terfenadine and astemizole are no longer marketed because of cardiovascular effects.

The first generation drugs produce their sedative effects by binding to the H-1 receptor, which is associated with wakefulness. Second generation drugs lack the CNS effects because of a difference in the ability of the drug to cross the BBB (Timmerman, 1999). Whether or not an antihistamine penetrates the CNS depends on its ionization, hydrogen-binding capacity and substrate affinity for P-gp. Some antihistamines enter the brain via a carrier-mediated system.

#### **Antibiotics**

Antibiotics are probably the most common group of drugs administered to animals, so it is not surprising that this class is frequently associated with adverse reactions in the CNS. The antibiotics implicated include primarily the beta-lactams but also fluoroquinolones (e.g. enrofloxacin) and metronidazole. There is an excellent review of antibiotic-associated convulsions by Wallace (1997), which explains the mechanisms and incidence in humans. The mechanism by which penicillins, cephalosporins, carbapenems and fluoroquinolones induce seizures is to inhibit binding of GABA to the GABA<sub>A</sub> receptor (Chow *et al.*, 2004). GABA ordinarily acts as an inhibitory CNS neurotransmitter, increasing chloride conductance.

#### Beta-lactams

The most important predisposing factor for antibiotics to cause seizures is renal insufficiency (Chow et al.,

2004); this is best documented for the beta-lactams (penicillins, cephalosporins, carbapenems). The increased risk of seizures is either related to an increase in the ability of these drugs to cross the BBB, caused by uraemia or decreased protein binding, or simply because these drugs accumulate to high concentrations in renal failure because they are not effectively excreted by the kidneys. The latter mechanism is probably more likely. The resultant high plasma concentration increases BBB penetration; indeed brain tissue fluid penicillin levels were higher in uraemic animals than normal controls (Chow et al., 2004). In a patient with renal failure the veterinary surgeon should observe animals for CNS toxicity after administration of any antibiotics, particularly beta-lactams. Dose intervals should be increased in accordance with the degree of compromised renal function. If CNS adverse effects are observed. the antibiotics should be discontinued or the dose interval increased.

#### Fluoroquinolones

There is a well known risk of CNS reactions from the fluoroquinolone antimicrobials (enrofloxacin, difloxacin, orbifloxacin, marbofloxacin). In humans other CNS disorders may be a predisposing factor (Wallace, 1997). In reality, oral administration is rarely associated with CNS toxicosis in animals. Rapid intravenous injections of quinolones should be avoided in seizure-prone animals. (Only one quinolone, enrofloxacin, is registered in an injectable form for small animals in the US; marbofloxacin is registered as an injectable in Europe.)

#### Metronidazole

Perhaps the most common antibiotic-associated neurotoxicity in animals is that from metronidazole (see above).

#### Summary

Figure 22.2 summarizes the drugs used to treat CNS disorders in dogs and cats.

Drug	Clinical use and comments	Recommended dose
Azathioprine	Used to treat immune-mediated diseases. Use cautiously and at much lower doses in cats	Dogs: 2 mg/kg orally q24h, followed by long-term therapy with 0.5–1.0 mg/kg orally q48h
Cefotaxime	Used for infections caused by <i>Enterobacteriaceae</i> that are resistant to other drugs and <i>Streptococcus</i> spp. Penetrates the CNS better than other cephalosporins	Dogs and cats: 30 mg/kg i.v., i.m. or s.c. q8h
Ceftazidime	Used for infections caused by Enterobacteriaceae or Pseudomonas spp. that are resistant to other drugs and Streptococcus spp. Penetrates the CNS better than other cephalosporins	Dogs and cats: 20–30 mg/kg i.v. q12h
Chloramphenicol	Used for some infections of the CNS. However, the activity against Gram-negative bacilli not good enough for treatment of infections caused by these bacteria	Dogs: 50 mg/kg orally q8h Cats: 50 mg/cat orally q8h

.2 Clinical use of drugs for CNS disorders in dogs and cats. CRI = constant-rate infusion. (continues)

Chapter 22 Drug therapy for diseases of the central nervous system

Drug	Clinical use and comments	Recommended dose
Clindamycin	Used to treat protozoal infections. However, efficacy has not been established	Dogs and cats: 11 mg/kg q12h or 22 mg/kg orally q24h
Cytarabine (cytosine arabinoside)	Used to treat CNS lymphoma	Dogs and cats: 50 mg/m² s.c. q12h for 2 days. Repeat every 3 weeks
Dexamethasone sodium phosphate	Used to treat CNS oedema and inflammation	Dogs and cats: 0.15 mg/kg i.v. q6h for 2–4 days
Fluconazole	Used to treat fungal infections of the CNS	Dogs: 10-12 mg/kg orally q24h Cats: 50 mg/cat orally q12h or q24h
Itraconazole	Used to treat opportunistic and invasive fungal infections of the CNS	Dogs and cats: 5–10 mg/kg orally q24h
Lomustine	Used to treat tumours of the CNS, particularly gliomas	Dogs and cats: 60-80 mg/m² orally q6-8 weeks
Meropenem	Used for infections of the CNS. Use for cases in which resistant bacteria may be suspected. Does not have the risk of CNS toxicity compared with imipenem	Dogs and cats: 5.5–11 mg/kg i.v. q12h
Methylprednisolone sodium succinate	Used to treat acute spinal cord trauma	Dogs and cats: <3h since injury: 30 mg/kg i.v. injection followed by 5.4 mg/kg/h CRI for 24 hours. If a CRI is not available then treat initially with 30 mg/kg i.v. within the first 8 hours of trauma, followed by 15 mg/kg i.v. at 2 and 6 hours after the initial injection. Thereafter 15 mg/kg i.v. q6h for 48 hours
Metronidazole	Treatment of CNS infections caused by <i>Bacteroides</i> (anaerobe). Caution that metronidazole can cause adverse CNS effects	Dogs and cats: 10–20 mg/kg orally q8h (most common is 15 mg/kg q12h)
Prednisolone	Used to treat inflammation of the CNS	Start with 2 mg/kg orally q12h. Gradually taper to lower doses until goal of 0.5 mg/kg orally q48h is achieved
Pyrimethamine	Treatment of protozoal infections of the CNS. Usually used in combination with sulfadiazine or other sulphonamide	Dogs and cats: 1 mg/kg orally q24h. Used with sulphonamide concurrently at a dose of 25 mg/kg orally q12–24h
Trimethoprim- sulphonamide	Used to treat protozoal infections	Dogs and cats: 15–30 mg/kg orally q12h

(continued) Clinical use of drugs for CNS disorders in dogs and cats. CRI = constant-rate infusion.

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# Radiation therapy of the nervous system

Donald E. Thrall

## Introduction

With the increasing availability of computed tomography (CT) and magnetic resonance imaging (MRI), intracranial masses are being detected with greater frequency. With regard to masses causing spinal cord compression, myelography has traditionally allowed for adequate identification but CT and/or MRI provide more accurate assessment of the extent of the disease. As a result of this more precise diagnostic and staging information, owners of animals with tumours affecting the brain or spinal cord are able to make more informed decisions about potential therapeutic interventions.

Surgery has been, and will likely remain, the mainstay of cancer treatment methods in dogs and cats, especially as it can also be a diagnostic procedure. However, tumours affecting the brain and spinal cord are often invasive and the anatomical complexity of the affected areas, along with the critical functions played by the involved tissues, often limits the extent of surgical resection and rarely allows tumour-free margins to be obtained following surgery. Also, some intracranial masses are located in regions where surgical intervention is not feasible without great risk of secondary complications, e.g. on the floor of the cranial cavity. Thus, radiation therapy, either alone or in combination with surgery, is regularly considered for patients with brain or spinal cord neoplasia. In this chapter the applications and results of radiation therapy for treatment of these tumours in small animals will be reviewed.

#### **Prescribing a radiation dose**

When radiation is administered to a tumour, an area of adjacent normal tissue is also irradiated. This is necessary because of the aim to include all peripheral margins of the tumour, including presumed microscopic extensions into normal tissue. It is the response of this adjacent normal tissue that limits the amount of radiation that can be administered. Radiation doses are selected based on the philosophy that treatment of the tumour must be aggressive and therefore some finite but small (<5%) probability of serious normal tissue complication is acceptable.

Once a radiation dose prescription has been decided upon, that dose is not given as one large exposure. Rather, the dose is divided into smaller doses called fractions that are typically administered on three

(Monday, Wednesday, Friday) or, preferably, five days per week (Monday through Friday) until the prescribed total dose has been delivered. Naturally, the chance that serious complications will develop is a direct function of the total dose of radiation, but it is also affected by the size of each of the fractions and the overall time wherein the total dose is administered.

# Radiobiology of the nervous system

Unique aspects of neural tissue necessitate some basic understanding of neural tissue radiobiology before radiation time—dose prescriptions are used for treatment of tumours affecting the central nervous system (CNS). Normal tissues can be divided into two basic types in terms of their response to radiation.

# **Acutely responding tissues**

Tissues that divide regularly, such as skin and mucosa, are referred to as acutely responding tissues. Complications developing in regularly dividing tissues as a result of radiation therapy, such as desquamation or mucositis, occur during or shortly after treatment and their development is directly related to the dose intensity.

Dose intensity is defined as the amount of radiation administered per unit time. Increased dose intensity can arise from use of larger doses per fraction and/or decreasing the time between fractions. As dose intensity increases, the total dose necessary to produce an acute reaction decreases. The more intensely the radiation dose is delivered, the more likely acute reactions will develop and the more severe they will be. Fortunately, complications arising in dividing tissues are manageable with suitable therapy and rarely limit administration of the prescribed radiation dose or compromise the quality of life.

#### Late-responding tissues

Tissues that do not divide regularly, such as bone, brain and spinal cord, are referred to as late-responding tissues. Complications occurring in late-responding tissues as a result of radiation therapy, such as necrosis or demyelination, occur many weeks to months, or even years, following completion of radiation therapy. As late-responding tissues are not dividing, development of complications is not related to the time over which treatment is given but rather is a function of the size of each individual dose fraction and the total dose. The larger the size of each fraction, the lower the total dose required to produce serious complications in

these late-responding tissues. Therefore, the probability of late complications may be reduced by use of small fraction sizes. Unfortunately, because of the critical functions provided by most late-responding tissues, including brain and spinal cord, complications are serious and always affect the quality of life adversely. Also, these complications are not treatable, thus their development should be avoided if at all possible. Contemporary radiation time—dose prescriptions are designed with a key objective being the avoidance of complications in late-responding tissues.

#### Radiation time-dose considerations

It is typical in the treatment of most types of human cancer for radiation to be given in 30-40 fractions of 1.8-2.0 Gy per fraction, for a total dose of 60-72 Gy. This fractionation scheme, which requires approximately 7 weeks to administer, was developed empirically and the relatively small fraction size is beneficial in minimizing the probability of complications arising in critical lateresponding tissues. Unfortunately, such protracted fractionation schemes are less feasible in veterinary radiation oncology practice because of: the requirement of anaesthesia for the administration of each radiation fraction; prolonged hospitalization for patients where outpatient treatment is not possible; and the associated cost to the pet owner. As a result, daily fraction sizes are typically increased to reduce overall time and expense of the total therapy. This results in a reduction in the total dose that can be administered without increasing the chance of complications in late-responding normal tissues such as bone, brain or spinal cord. Unfortunately, brain and spinal cord are also more sensitive to the effects of radiation than other non-proliferative tissues such as bone or muscle. Therefore, a further reduction in total dose will also be needed to avoid serious brain or spinal cord complications, especially if large volumes of these structures are irradiated.

At North Carolina State University, a fractionation scheme of nineteen 3.0 Gy fractions given daily Monday through Friday, for a total dose of 57 Gy, has been used for many years in the treatment of most malignant tumours outside the nervous system. This dose prescription occasionally results in moderate to severe acute reactions such as mucositis and desquamation, particularly when large tissue volumes are irradiated, but serious complications in late-responding tissues are extremely rare. However, given the serious consequences of complications arising in brain and spinal cord, and the more limited overall radiation tolerance of these tissues, the total dose is reduced to 48 Gy by using 16 rather than 19 fractions when brain or spinal cord must be included in the treatment field. This fractionation scheme has been well tolerated with few (<5%) documented instances of radiation-induced complications.

Another approach to avoiding overly protracted radiation time—dose prescriptions is to use larger fraction sizes, in the 4.0–4.5 Gy range, given three times a week rather than five. Though this reduces the total number of radiation fractions, the larger fraction size imposes further limits on the total dose tolerable by late-responding normal tissues, such as brain and spinal cord.

Finally, it is questionable whether the tolerable total dose delivered by use of either 3.0 Gy or larger fractions is adequate to control most macroscopic tumours affecting the brain or spinal cord. More sophisticated treatment methods involving more conformal administration of the radiation or combined therapies using surgery or other approaches may be necessary before tumour control at these sites is optimized.

# **Reported studies**

The following paragraphs summarize clinical reports describing results obtained from irradiation of various tumours affecting the brain or spinal cord. Although useful for some information, reports dealing with very small numbers of patients have not been discussed because of the probability that observed responses may not be typical of the patient population at risk. Additionally, most information on the radiation response of tumours affecting the brain or spinal cord comes from retrospective studies. Results of retrospective studies must be interpreted with caution because of the lack of organized follow-up and the non-randomized manner in which treatments are assigned. Absolute survival information from trials involving small patient numbers, or retrospective studies, must be viewed with caution and all such trials should be viewed as hypothesis-generating exercises rather than the final word with regard to counselling pet owners.

#### **Brain tumours**

#### Intracranial mass

There is probably less known about the radiation response of canine and feline brain tumours than any other type of tumour in veterinary oncology practice. This uncertainty has resulted from the failure to obtain definitive histopathological diagnosis in all patients with brain masses undergoing radiation therapy, a lack of information on the natural course of the disease if untreated, and the difficulty in ascertaining whether recurrent neurological signs following irradiation are due to tumour recurrence, radiation neuropathy or intercurrent disease.

It seems ill-advised to administer radiation therapy to patients with a brain mass when the definitive histopathological diagnosis is unknown. However, given the potential morbidity and cost associated with obtaining a definitive diagnosis prior to treatment, patients are sometimes irradiated without definitive evidence that the mass is in fact neoplastic. Though certain tumours have relatively specific imaging characteristics, accurate diagnosis of tumour type based on these features is not possible because of similarity in imaging appearance for some tumours (Kraft et al., 1997). This is a unique situation in veterinary oncology. It is common practice for owners to be given the option of biopsy of a brain mass, although some may refuse when the morbidity and cost arising from the biopsy are compared with those associated with radiation therapy.

Recently, stereotactic CT-guided biopsy frames have been adapted for veterinary use (Koblik et al.,

1999; Giroux et al., 2002) and it is highly likely that as their use becomes more widespread a higher fraction of patients with a brain mass will have a biopsy prior to treatment. Caution should be exercised, however, when basing diagnosis of a brain mass on a sample obtained by needle aspiration. Fine-needle aspiration can be used to determine the presence of neoplasia in the brain but is not as definitive as Tru-cut biopsy in determining specific tumour type (Platt et al., 2002). A biopsy smear technique using a stereotactic frame has been shown to be useful for rapid accurate intraoperative diagnosis of many primary nervous system tumours (Vernau et al., 2001). At this time, however, inclusion of patients without a definitive diagnosis in reports of treatment efficacy diminishes the ability to use response information to counsel animal owners.

Comparing therapies: Survival was analysed in 86 dogs with an intracranial mass treated with a variety of modalities (Heidner et al., 1991). Administered therapies were variable and included surgery, cobalt irradiation, chemotherapy and hyperthermia, alone and in combination, as well as supportive care alone. Dogs receiving radiation usually received 3.8 or 4.0 Gy fractions and a total dose of 46–48 Gy. Of the 86 dogs, 69 had histological confirmation of tumour type, whereas 17 had CT evidence of a tumour.

Factors associated with a more favourable outcome were: use of radiation *versus* surgery or supportive treatment; single *versus* multifocal brain involvement; mild initial neurological impairment; and meningioma *versus* other tumour types. Results of this study suggest that radiation may be of value for treatment of intracranial tumours, that initial clinical severity and the number of brain regions involved are related to outcome, and that meningioma may respond more favourably than tumours of the neuropil.

**Radiation alone:** In 2000, results from a retrospective trial of irradiation of canine intracranial masses were reported (Spugnini *et al.*, 2000). A total of 29 dogs with intracranial signs and imaging findings suggestive of a tumour were irradiated with cobalt photons; 28 of the dogs received the same radiation time—dose prescription of 48 Gy in 3.0 Gy fractions, without surgery.

Though follow-up was sporadic, median survival was 250 days (range 21–804). Twenty-two dogs (76%) died with progressive neurological signs but it was not determined whether these were due to tumour progression or radiation necrosis. Based on the median survival, results of this study suggest a limitation of radiation alone for treatment of gross intracranial tumour. Results also illustrate the problem of determining whether relapse following irradiation is due to tumour recurrence or radiation effects unless post-mortem examinations are conducted.

*Hypofractionated radiation:* In 1999, results from irradiation of intracranial masses in dogs using a hypofractionated fractionation scheme were published (Brearley *et al.*, 1999). Dogs were treated once weekly and the total radiation dose was 38 Gy. Though the fraction size varied between dogs, the mean fractional

dose was approximately 7.5 Gy. As mentioned above, the CNS is very sensitive to such large doses per fraction. Using an accepted isoeffect formula (Withers et al., 1983), it can be shown that a total dose of 38 Gy administered in 7.5 Gy fractions is biologically equivalent to approximately 90 Gy given in 2.0 Gy fractions. The probability of brain necrosis resulting from a dose of 90 Gy in 2.0 Gy fractions would be nearly 100%.

Interestingly, median survival was 44 weeks (range 0.1–72 weeks), one of the longest reported. However, extreme caution must be exercised when administering this coarsely fractionated protocol to patients in a definitive setting as the probability of serious complications is very high. It is difficult to interpret the results of this study completely, as histopathological diagnoses were not available for any patient, the severity of initial neurological status was not clear, and histopathological assessment of the effect of this hypofractionated protocol on normal brain was not accomplished.

Randomized trial: The only randomized trial of radiation therapy for canine intracranial masses was reported by Thrall et al., 1999. It involved evaluation of increased tumour temperature (hyperthermia) combined with irradiation as a means to enhance tumour response. A total of 45 dogs with neurological signs and imaging findings consistent with an intracranial tumour were studied. One advantage of this study was rigorous follow-up imaging assessment of tumour response to treatment. Radiation dose ranged from 44 to 60 Gy, given in daily 2.0 Gy fractions. Twenty-four dogs had meningioma and 5 had a glioma. The remaining 16 dogs were either alive at study end (7), had other tumour types (4), had no tumour at necropsy examination (3), or did not have a necropsy examination (2).

Hyperthermia was ineffective in prolonging survival. One- and 2-year survival probabilities, thus reflecting radiation response alone, were approximately 0.42 and 0.27, respectively. Overall median survival was approximately 200 days. Results from this study indicate that hyperthermia was an ineffective method of enhancing radiation response; the study supports the median survival following irradiation of a canine intracranial mass to be approximately 200 days. The range of radiation doses used, and some toxicity associated with the hyperthermia procedure, complicate interpretation of the results. Interestingly, in a Phase III trial of radiation and hyperthermia for treatment of human glioma, hyperthermia was shown to result in statistically significant improvement in survival when combined with radiation when compared with radiation alone (Sneed et al..1998). Nevertheless, the radiation response of gliomas in humans remains one of the most dismal of all tumour types.

#### Meningiomas

As meningiomas are often located peripherally, surgical removal is perhaps attempted more often for this tumour than for all other intracranial tumour types.

**Surgery alone:** In cats, long-term survival has been documented following surgical resection of meningioma. In 1994, results of the treatment of 42 cats were

published (Gordon *et al.* 1994). Although immediate perioperative mortality was relatively high (8 of 42 cats) and another 10 cats had an unimproved or a worsened neurological status, overall survival was 71% at 6 months, 66% at 1 year, and 50% at 2 years.

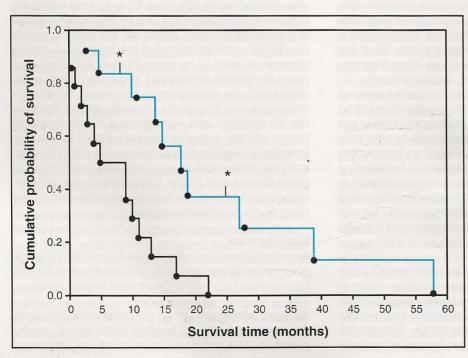
In another study, 11 of 17 cats did not develop evidence of tumour recurrence within 18–47 months of surgery (median = 27 months) (Gallagher *et al.*, 1993). Thus, surgery alone may be curative in some cats with meningioma but assessment of completeness of tumour excision is recommended because cats with residual microscopic tumour would theoretically benefit from postoperative irradiation.

Postoperative irradiation: With regard to canine meningiomas, information in a recent study suggests that use of postoperative irradiation significantly improves survival (Axlund et al., 2002). Survival in 26 dogs treated with either surgery (14) or surgery and postoperative irradiation (12) was evaluated, and found to be significantly longer in dogs receiving both surgery and postoperative irradiation: median survival of 7 versus 16.5 months (Figure 23.1). Irradiated dogs received 40-49.5 Gy but the fraction size was not specified and post-mortem information on brain necrosis was not available. It is not clear how the decision was made with regard to which patients received postoperative irradiation and this non-random assignment of treatment may have biased the population of patients in each group and thus affected the survival times. Nevertheless, these results support the use of postoperative irradiation in dogs undergoing meningioma resection. What is not known with certainty is the median survival of dogs with meningioma treated only with radiation; this would aid in evaluating the need for surgical removal of a portion of the tumour.

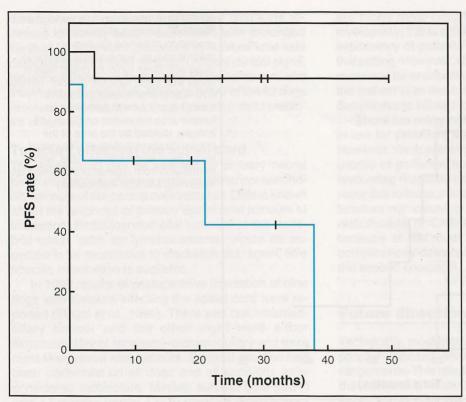
PCNA labelling: There is great interest in assessing the microenvironmental characteristics of tumours to identify factors that may be used to counsel owners more accurately, or to identify tumours suitable for specific antineoplastic interventions. Tumour proliferation is one factor that has been studied in an attempt to identify tumours that may be at higher risk of treatment failure due to rapid tumour cell proliferation. Using immunohistochemical detection of an endogenous marker of tumour cell proliferation rate (PCNA), dogs with a rapidly proliferating meningioma had significantly shorter progression-free survival (PFS) than dogs with slowly proliferating tumours (Theon et al., 2000). Twenty dogs received postoperative irradiation following meningioma resection. Overall median PFS was 30 months. Dichotomizing the dogs based on the median PCNA labelling fraction proved significant as median PFS in dogs with rapidly proliferating tumours was approximately 20 months compared with >50 months in dogs with slowly proliferating tumours (Figure 23.2). Thus, assessment of PCNA labelling in resected meningioma specimens will be useful for owner counselling and also for identification of dogs at higher risk of early failure. These high-risk dogs may then be considered for other more aggressive therapies, such as higher radiation dose, more accelerated administration of radiation dose, or combined radiation and chemotherapy.

### Pituitary tumours

More detailed information is known regarding the response to irradiation by canine pituitary macrotumours (masses >1 cm in diameter) than by all other types of intracranial mass. The anatomical location of the canine pituitary gland and the suprasellar location of pituitary tumours make successful surgical removal of macrotumours extremely difficult (Lantz et al., 1988); there is thus a clear indication for irradiation.



Cumulative 23.1 probability of survival as a function of time after treatment for canine meningioma treated with surgery alone (black line) or surgery followed by irradiation (blue line). Median survival is approximately 7.0 and 16.5 months, respectively, suggesting a role for postoperative irradiation in canine meningioma patients. \* denotes censored data point. (Reprinted from Axlund et al., 2002, with permission from Journal of the American Veterinary Medical Association)



Progression-free survival (PFS) as a function of time after treatment for canine meningioma based on the proliferative capacity of the tumour. Survival of dogs with rapidly proliferating tumours (blue) is shorter than that of dogs with slowly proliferating tumours (black). Proliferative capacity was based on immunohistochemical quantification of PCNA. (Reprinted from Theon et al., 2000, with permission from Journal of the American Veterinary Medical Association)

A highly informative description of factors associated with favourable outcome following irradiation was published in 1998 (Theon and Feldman, 1998). A total of 24 dogs with a pituitary macrotumour and associated neurological signs were studied. All received the same radiation time-dose prescription of 48 Gy, given in thrice-weekly 4.0 Gy fractions. There were significant positive relations between relative tumour size and both endogenous plasma adrenocorticotropic hormone (ACTH) concentration and the severity of neurological signs. Overall median PFS was 13.1 months (± 8.3 months). Dogs with larger tumours (Figure 23.3) and endocrinologically inactive tumours (Figure 23.4) had shorter survival times than dogs with small or active tumours. These results support the use of irradiation in dogs with pituitary macrotumours. Dogs with small and/or endocrine active tumours are likely to be the longer responders. Dogs with large and/or endocrine inactive tumours should be considered for more aggressive therapy, such as higher dose, or more conformal radiation techniques. The radiation timedose prescription used in this study was suboptimal because of: the large fraction size (predisposes to radionecrosis); and use of only three fractions per week (allows for more tumour repopulation during treatment). Significant radiation changes in normal brain were found in many dogs from this study, especially in those with large tumours necessitating large radiation fields. Results from a more finely fractionated and/or conformal protocol may be improved.

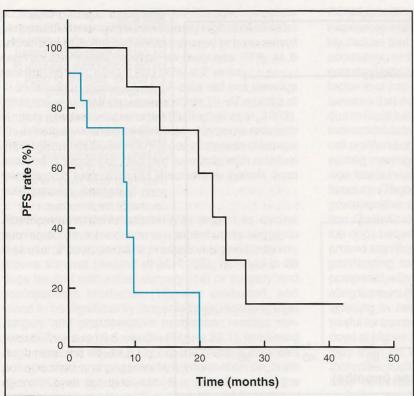
Occasionally, pituitary irradiation is considered for treatment in patients with macroadenoma and pituitary hyperfunction but with no associated neurological dysfunction. In 1998, six dogs with pituitary-dependent

hyperadrenocorticism and a detectable pituitary mass, but no evidence of mass-associated neurological dysfunction, were treated using pituitary irradiation (Goossens et al., 1998a). Each dog received 44 Gy, delivered in eleven 4.0 Gy fractions on a thrice-weekly schedule. Plasma ACTH concentration was measured before, and at regular intervals after, completion of radiation therapy. Pituitary imaging was repeated one year after irradiation. Radiotherapy did not result in adequate control of clinical signs of hyperadrenocorticism in 5 of the 6 dogs, but the size of the pituitary tumours was dramatically reduced. Thus, pituitary irradiation in dogs with macroadenoma and pituitary hyperfunction, but not neurological dysfunction, may be useful in preventing the development of neurological signs, but will not be effective in normalizing the endocrinopathy.

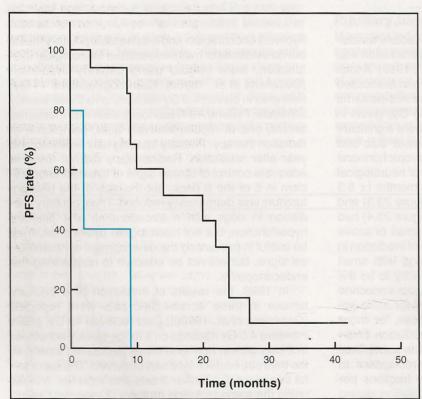
In 1998, the results of irradiation of a pituitary tumour in three acromegalic cats were reported (Goossens *et al.*, 1998b). Cats received 48 Gy, given in twelve 4.0 Gy fractions on a thrice-weekly schedule. In 2 cats growth hormone levels decreased slowly; in the third cat, no decrease was observed. The successful treatment of a further 5 cats was reported in 2002 using the same radiation protocol (Kaser-Hotz *et al.*, 2002a). Thus, pituitary irradiation may be effective in decreasing pituitary hyperfunction in some cats, but if improvement of endocrinopathy occurs the rate of change will be in the order of years.

#### Lymphoreticular tumours

There is essentially no information on the outcome of brain lymphoma to irradiation. In general, lymphoid tumours are very responsive and irradiation of solitary



Progression-free survival as a function of time after irradiation of canine pituitary macrotumours. Survival was shorter in dogs with large tumours (blue) than in those with small tumours (black). Tumour size was characterized as relative tumour size, defined as the largest tumour area visualized on CT or MR images, divided by the area of the cranial cavity at that level. (Reprinted from Theon and Feldman 1998, with permission from Journal of the American Veterinary Medical Association)



Progression-free survival as a function of time after irradiation of canine macrotumours. Survival was shorter in dogs with endocrinologically inactive tumours (blue) than in those with active tumours (black). (Reprinted from Theon and Feldman 1998, with permission from Journal of the American Veterinary Medical Association)

brain lymphoid masses would be expected to be associated with a favourable outcome. In animals it is not known whether radiation therapy should be combined with chemotherapy in patients with brain lymphoma, but in humans a survival advantage has been reported from a combined therapy approach (Ferreri et al., 2002).

Though not technically a neoplastic process, granulomatous meningoencephalitis (GME) may result in mass lesions in the brain and or spinal cord that are poorly chemoresponsive and are also not amenable to surgery. In 1998, prognostic factors for 42 dogs with GME were reviewed (Muñana and Luttgen, 1998). Signalment, clinical signs, cerebrospinal fluid

derangements, treatment and survival time were reviewed to identify factors associated with prolonged survival. A significant difference in survival time was demonstrated for focal *versus* multifocal clinical signs, neurolocalization of focal signs to the forebrain, and treatment with radiation. Although only 7 of the 42 dogs received radiation, it was the only independent predictor of survival.

### Tumours affecting the spinal cord

The spinal cord can be affected by primary neural tumours, tumours of nerve roots, or primary or secondary tumours of the paraspinal structures. Little is known about the response of primary spinal cord tumours to irradiation. Reticuloendothelial tumours of the vertebral canal, such as lymphosarcoma, would be expected to be responsive to irradiation but, again, little specific information is available.

In 1992 results of postoperative irradiation of nine dogs with tumours affecting the spinal cord were reported (Siegel *et al.*, 1996). There was one intramedullary tumour and the other eight were either extramedullary or intradural—extramedullary and were most likely nerve root tumours. Surgical excision had been performed on all dogs and all excisions were considered incomplete. Median survival time (MST) was 17 months (range 12–70 months). Results suggest that postoperative irradiation of incompletely resected nerve root tumours may result in a satisfactory outcome, but more work will be needed to determine likely MST more precisely.

Finally, there is essentially no information on the radiation response of paraspinal tumours. Some general concepts may be used to guide decision-making. Macroscopic paraspinal mesenchymal tumours, such as vertebral body osteosarcoma, are unlikely to be controlled permanently by irradiation. Macroscopic solitary paraspinal reticuloendothelial tumours, such as vertebral body plasma cell tumours, would have a much better prognosis and, if pathological vertebral fracture can be avoided, the chance for long-term remission is likely to be high.

#### **Palliative irradiation of the CNS**

When permanent control of a primary tumour is unlikely but some temporary relief of discomforting clinical signs is desired, palliative irradiation may be useful. Palliative irradiation involves administration of a small number of fractions of radiation, with the sole intent being temporary resolution of clinical signs associated with pain or dysfunction, not prolongation of life (Thrall and LaRue, 1995).

In veterinary medicine, palliative radiotherapy has mainly been used for appendicular osteosarcoma (Ramirez et al., 1999) but its use for soft tissue tumours has also been reported (Siegel and Cronin, 1997). Though there are not specific reports of the use of palliative radiation for CNS tumours, there is no reason why such cannot be accomplished. Typically, palliative radiotherapy employs larger doses per fraction, often in the 4.0–10 Gy range. Though these large fractions

are much more likely to result in brain necrosis or myelopathy, this is of less concern given the limited life expectancy of patients receiving radiation in a palliative setting. However, should an unexpected long-term remission be encountered, it must be kept in mind that the patient is at much higher risk for development of complications related to the irradiation.

There are many radiation time—dose prescriptions in use for palliation; these will not be reviewed here. However, some prescriptions are designed to allow the course of palliation to be repeated should an initial favourable response be obtained but the clinical signs recur due to tumour relapse. Though this is suitable for tumours not involving the CNS, repeating palliative radiotherapy of CNS tumours is not recommended because of the much greater possibility of serious complications developing relatively quickly following the second course.

#### **Future directions**

Technically, most brain masses are irradiated with two parallel opposed fields or four-field orthogonal arrangements. This results in a cuboidal volume of tissue that receives a relatively homogenous dose. Though adequate in principle, the volume of normal brain commonly included in the high-dose region limits the dose of radiation that can be given to the tumour. Recently, various technology has been developed that will allow more conformal delivery of the radiation dose providing, in principle, a method to increase the dose to the tumour while decreasing the dose to normal brain.

# Stereotactic dosing

In 2001 results from treatment of three canine brain tumours using radiosurgery and a stereotactic head frame were reported (Lester et al., 2001). Radiosurgery involves administration of a single relatively large dose of radiation (10-15 Gy) to the tumour in a highly conformal manner. A stereotactic headframe is attached to the patient and the coordinates of the headframe and visible tumour are recorded in threedimensional space using CT imaging. Then, multiple non-coplanar beams of radiation are focused stereotactically on the target, using the image-based computer system. The radiation source rotates in an arc around the tumour, with multiple non-coplanar arcs used for each isocentre. This results in a highly conformal distribution of the radiation dose to the tumour, and substantial reduction in dose to adjacent normal brain. The three dogs treated in this report survived for a period comparable to reports of dogs with intracranial masses treated with conventional radiation techniques. One major advantage of this technique, other than reduced dose to normal brain, is that only one treatment is given and therefore anaesthesia is required only once. However, the technique is labour- and time-intensive and requires sophisticated technology and high-level physics support. Also, imaging is relied upon to delineate tumour margins precisely and the accuracy of such determinations is still being debated.

### Proton radiotherapy

Another technology that has been used in veterinary radiation oncology but has not yet been applied to treatment of canine brain tumours is proton radiotherapy. Protons are charged particles (hydrogen nuclei) and are characterized by enhanced ionization and, thus, enhanced biological damage when they come to rest in tissue. It has been shown that use of pencil-beams of protons delivered from multiple angles results in highly conformed radiation dose distributions in canine tumours (Kaser-Hotz et al., 2002b). Therefore, this presents another method whereby brain tumour dose may be increased with reduced probability of radionecrosis in adjacent brain. However, proton radiation facilities are very rare and also require intensive physics support for accurate treatment delivery.

It is highly likely that such innovations in radiation therapy technology will make their way into veterinary radiation oncology practice. However, it is highly unlikely that radiation therapy alone will ever be the firstline treatment for macroscopic brain masses. It is imperative that forward-thinking veterinary surgeons get involved in looking for more inventive methods to improve outcome other than simply giving a higher radiation dose. Effort must be directed at identification of molecular targets and for introduction of innovative adjunctive therapies such as gene therapy and liposomal delivery of various compounds.

### Summary

It is unfortunate that one must conclude that very little is known about the radiation response of tumours affecting the brain and/or spinal cord in animals. This results from the retrospective, non-randomized nature of essentially all clinical reports describing treatment results for these tumours. Additionally, numbers of patients in each study are extremely small. These factors mandate that very little significance be placed on absolute survival or remission times quoted regarding treatment of brain and/or spinal cord tumours. It is common in veterinary medicine for numerical endpoints (e.g. survival times that are published based on retrospective assessment of an insignificant number of patients) to become engrained in the mindset and never be re-evaluated in a more controlled prospective setting. Veterinary surgeons must organize their efforts and embark on more prospective assessment of various approaches. Until this is accomplished, the quality of the available data will not become more robust.

The following conclusions can be drawn about the utility of radiation for treatment of tumours affecting the brain or spinal cord:

- We do not know the relative value of radiation therapy given alone or in combination with surgery for treatment of tumours of glial origin
- There is a suggestion that radiation combined with surgery is more effective than surgery alone for treatment of canine meningioma, but the relative value of radiation alone in this setting is

- unknown. There are data suggesting that the proliferative capacity of meningiomas is related to outcome following radiation combined with surgery
- Some pituitary tumours appear to respond well to irradiation and there are some data supporting the negative influence of relative tumour size and lack of endocrine activity on outcome
- There are no data on the response of reticuloendothelial tumours of the brain to radiation therapy. Based on the high radiocurabiltiy of solitary lymphoid tumours in humans, animal patients with a similar tumour may respond favourably. Dogs with GME also appear to have a favourable prognosis provided involvement is focal
- There are essentially no reliable data enabling accurate counselling of owners of animals with spinal/vertebral tumours. Some general principles, obtained from other animal tumours and also from human studies, are probably accurate. These are:
  - Macroscopic mesenchymal paraspinal or nerve root tumours are not likely to be controlled permanently with radiation
  - Postoperative irradiation of microscopic mesenchymal paraspinal or nerve root tumours is expected to be superior to incomplete resection alone
  - Macroscopic paraspinal reticuloendothelial tumours are likely radiosensitive, and definitive irradiation may be justifiable in a large percentage of patients.

Further discussion can be found in the BSAVA Manual of Canine and Feline Oncology, 2<sup>nd</sup> edition.

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# Nursing and rehabilitation of the neurological patient

John Sherman and Natasha J. Olby

#### Introduction

Physical rehabilitation plays an essential role in the management of human neurological diseases. It is recognized that although axonal regeneration can occur in the peripheral nervous system (PNS), regeneration in the central nervous system (CNS) is usually unsuccessful and recovery is largely due to the plasticity of the system (Jeffery and Blakemore, 1999).

Plasticity refers to the alteration in the role of the neuron caused by changes in synapse density and type, as well as the sprouting of axons to make contact with other local targets. This process allows surviving neurons to assume new functions and is enhanced by repeated stimulation of the pathways.

It is also known that disuse and immobilization of limbs results in loss of muscle mass, muscle contractures, and deterioration in joints and associated structures. Physical therapy plays a critical role in limiting and reversing these effects and maximizes the extent of functional recovery.

To date, there are few published studies on the use of physical rehabilitation in veterinary medicine; most of these have focussed on patients with orthopaedic disease (Marsolais et al., 2002; Steiss, 2002; Gandini et al., 2003). This is because historically it has been unusual for physical therapy to be recommended routinely as part of a neurological treatment plan. However, the merit of rehabilitation is being increasingly recognized, leading to the establishment of dedicated veterinary rehabilitation centres and specialist training for veterinary physical therapists. Moreover, methods of measuring functional outcomes, such as the use of goniometry to measure range of motion (Jaegger et al., 2002), kinematic analysis of gait (McLaughlin, 2001) and expanded gait scoring systems (Olby et al., 2001). are currently being developed and will facilitate objective evaluation of the benefits of rehabilitation.

This chapter discusses the development of an individualized treatment plan based on patient assessment, anticipated secondary health problems, and physical therapy techniques available.

# **Patient assessment**

Assessment of the individual neurological patient is critical for the rehabilitation process. The evaluation should involve the patient, owner (the needs of both the

patient and owner have to be considered) and the referring veterinary surgeon (if applicable).

At the end of the assessment the clinician should have a thorough understanding of the:

- · Patient's previous and current ailments
- Patient's normal physical activities and psychological status
- Owner's desired and anticipated expectations of outcome
- Owner's ability to provide time and expertise
- Specific details of the presenting neurological problem.

When assessing the presenting neurological condition, specific details to consider include:

- · The duration and progression of clinical signs
- Localization of the neurological lesion
- · The type and severity of pathology present
- Treatments including surgeries performed
- Any changes in the neurological status since those procedures.

In the case of common neurological diseases, such as thoracolumbar intervertebral disc herniations and caudal cervical spondylomyelopathy, published information about the typical time course and level of recovery can be referred to in determining the expectations for recovery (see Chapters 14 and 15).

#### **Treatment plan**

The treatment plan can be developed as a programme for:

- · An owner, with guidance
- A combination of the owner and primary veterinary surgeon
- A dedicated facility for animal physical rehabilitation on an inpatient or outpatient basis.

Medical points to consider when deciding which programme is most suitable include: whether the animal is ambulatory; whether it is continent; and the presence of additional health problems. In addition, there must be enough people available to enable the animal to perform exercises with no risk of further injury.

Regardless of the option chosen, the principles of treatment are the same.

- Appropriate supportive care must be provided (see below) both to prevent secondary health problems and to encourage an environment for healing to take place. A good functional outcome depends on the integrity of the nervous system and the overall health of the patient. Prevention of secondary diseases is much easier than treating them and is an important aspect of rehabilitation.
- Efforts should be made to decrease the progression of pathology within the nervous system.
- Functional recovery should be enhanced by designing a treatment plan that focuses on preservation of muscle mass and range of motion, maximizing the plasticity of the nervous system and includes proprioceptive neuromuscular training to promote recovery of a normal gait (Figure 24.1).

It is important that appropriate diagnosis and treatment of underlying problems is sought if not already addressed.

# **Supportive care**

### Bladder and bowel management

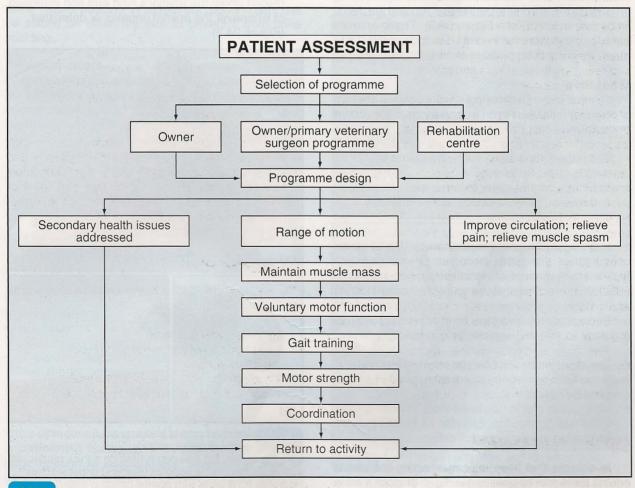
#### Urination

Animals that have spinal cord disease or primary autonomic dysfunction (e.g. dysautonomia) may be unable to urinate voluntarily or effectively (see Chapter 18). These animals are at risk of:

- Developing urinary tract infection (UTI)
- Damaging their bladder wall as a result of overdistention
- Damaging their upper urinary tract in severe cases.

It is prudent to assume that paraplegic animals are unable to urinate until proven otherwise.

Such animals should have their bladders expressed manually 3–4 times a day. Drugs can facilitate manual expression in animals where it is difficult, by relaxing the external urethral sphincter (e.g. diazepam at 0.25–0.5 mg/kg orally 20 minutes prior to expression) and the internal urethral sphincter (e.g. phenoxybenzamine at 0.5 mg/kg orally q8h–q12h). Care must be taken: phenoxybenzamine is an alpha-adrenergic antagonist and thus, at high doses, hypotension can result.



Developing a treatment plan for the neurological patient.

In animals where manual expression is not possible repeated aseptic catheterization may be necessary (see Chapter 18). This procedure is not always possible in females, and in these cases a soft Foley catheter should be placed and maintained in an aseptic manner.

Routine placement of indwelling catheters is not recommended, if it can be avoided, as it increases the chance of an antibiotic-resistant UTI developing. An additional risk in male cats is iatrogenic trauma to the bladder wall. Indeed, the authors have had to transfuse male cats that have developed trauma-induced haematuria as a result of having an indwelling tom-cat catheter placed for more than 2 days.

- Urine should be monitored daily for changes in odour and colour.
- Urine dip sticks can be used to check protein content and for the presence of blood.

If a UTI develops, the antibiotic treatment prescribed should be based on the results of urine cultures.

In a study on dogs with severe spinal cord injuries, 24% that recovered voluntary motor function developed UTIs within the 3 months after the injury (Olby *et al.*, 2003).

Animals with lower motor neuron (LMN) paralysis of their bladder tend to leak urine constantly, causing irritation to the skin in the perineal region and the pelvic limbs (urine scald) (see Figure 24.3). These animals almost always have persistent UTIs and are difficult to manage, but regular bladder expression can help.

#### Defecation

Innervation of the gastrointestinal tract allows animals to defecate reflexively even when they have spinal cord transections.

- The normal defecation reflex is initiated by stretch of the rectal wall.
- Voluntary control of the external anal sphincter and the abdominal muscles allows voluntary control of defecation.

In animals with upper motor neuron (UMN) spinal cord injuries this reflex becomes overactive, such that a small amount of rectal distension results in initiation of defecation that cannot be prevented (Holmes *et al.*, 1998).

Recumbent animals must be checked and cleaned regularly so that they are not lying in faeces.

- The defecation reflex can be initiated in recumbent animals by direct stimulation of the perineal region.
- Changes in diet to decrease stool volume, and establishing a routine, can also be helpful in controlling the frequency of defecation.

In animals that have lesions affecting the cauda equina there can be constant leakage of stool. This is very difficult to deal with but can be addressed by:

- Feeding a low residue diet that decreases stool volume
- · Frequent cleaning of the animal
- · Use of appropriate bedding
- Drying the perineal skin and applying a waterproof barrier cream.

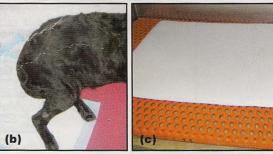
Toilet training is so imprinted on some dogs that they are extremely unlikely to urinate or defecate indoors. It is important that each animal is given the opportunity to perform these activities in a situation and on a surface to which it is accustomed.

#### Bedding

Suitable bedding depends on the circumstances.

- Animals that can maintain sternal recumbency should be on a grate or a sling bed that allows drainage of urine away from the animal (Figure 24.2).
- Such flooring and beds do not always provide adequate padding for recumbent large-breed, thin animals. These animals should be placed on a porous, well padded surface so that the skin does not get moist and urine can drain away.
- If the animal is trying to rise, it is important that the floor is non-slip and that the area is confined to minimize the risk of falling.
- Multiple absorbent disposable pads can be placed under the animal's hind end and disposed of whenever the animal urinates or defecates (Figure 24.2).





Various forms of bedding. (a) A sling bed made of netting to allow fluids to drain away from the animal. (b) This dog is lying on a thick rubber mat with easily removable nappies (diapers) underneath its hind end. (c) A grate with porous bedding material on it for recumbent animals.







Dermatological consequences of neurological disease.

(a) This dog has severe urine scalding from 2 days of recumbency and inability to urinate, combined with urine overflow and a urinary tract infection. (b) This chronically paraplegic dog has been licking the dorsal aspect of its tarsus. (c) A chronic decubital ulcer over the calcaneus.

#### Skin care

Animals with neurological diseases develop skin problems as a result of recumbency, incontinence, sensory dysfunction and boredom (stereotypical behaviour). Problems range from mild skin irritation to decubital ulcers, severe urine scald and self-mutilation (Figure 24.3).

General skin care of the recumbent animal involves keeping the animal clean and dry. Incontinent animals with long hair coats should be clipped in the perineal and inguinal regions so that the underlying skin can be cared for appropriately. However, if possible, the coat should be left over the common pressure points to provide some natural padding. A waterproof barrier cream can be placed on clean dry skin to protect it from urine scalding.

#### **Decubital ulcers**

These develop over pressure points such as the greater trochanter of the femur as a result of prolonged periods of obstruction to the local circulation. Ulcers can develop in small as well as large dogs, but are unusual in cats.

The affected tissue undergoes ischaemic necrosis, and inconsequential lesions can rapidly develop into large, deep ulcers as the dead tissue sloughs (see Figure 24.3). Prevention of ulcers is better than cure, and this can be achieved by:

- The regular turning of recumbent animals (every 4–6 hours)
- Pressure point massage to promote circulation every 4–6 hours
- Suitable bedding
- Hydrotherapy
- Elevation of 'at-risk' pressure points using 'doughnuts' of padding
- Daily sling-supported walking ('slinging') of recumbent animals so that they have a period when they are in a normal standing position.

'Doughnuts' can be made from bubble wrap rolled into a cylinder and then into a circle, and covered with a conforming bandage. The 'doughnut' should be large enough to surround and elevate the area of concern whilst maintaining circulation to the margins of the ulcer.

- The use of slings, hoists and carts to get dogs into a normal standing position should be attempted at least twice a day (Figure 24.4), although this may not be possible in animals that have suffered severe trauma.
- In general, dogs are placed in their cart for as long as they will tolerate it: this can range from a minute to half an hour, depending on the stage of recovery and the individual.
- When the patient puts its entire bodyweight on the sling instead of supporting it themselves or shows signs of discomfort, it should be taken down from the sling.





Carts for (a) paraplegic and (b) tetraplegic animals. Note that the paraplegic dog is wearing boots on its hind feet to protect them from abrasions (arrowed).

The ischial tuberosities produce a pressure point that needs to be carefully monitored in paraplegic dogs that sit upright and rock back on to these bones (Figure 24.5). Although a 'doughnut' can be made for such dogs to sit on, they will usually move off it very quickly. Anxiolytic drugs (e.g. diazepam 0.25–0.5 mg/kg orally up to 3 times a day) can be tried in order to make these animals lie down. It is also important to sling them intermittently to take the weight off the affected area.

Treatment of decubital ulcers includes:

- Providing appropriate bedding and pressure relief
- Clipping the hair to show the full extent of the problem
- Surgical debridement of ischaemic tissue
- The application of wound dressings to promote healing by second intention
- Massage of the surrounding area to encourage blood flow.

A balanced diet is also important for tissue healing.



Typical pose of a dog with a caudal lumbar lesion, causing it to sit on its ischial tuberosities.

#### Self-mutilation

This occurs in animals with a complete lack of sensation (i.e. deep pain negative animals), as a result of paraesthesias, and in bored or stressed animals as a stereotypic behaviour.

Self-mutilation has been described in animals with neuropathies as a result of lumbosacral (LS) disease, trauma and inherited sensory neuropathies (Tarvin and Prata, 1980; Cummings *et al.*, 1983; Jacobson and Schrader, 1987).

If an animal starts to lick or bite a part of its body, this should be prevented by the use of an Elizabethan or bite collar. In addition the patient should be assessed for an obvious trigger (e.g. a decubital ulcer) and treated appropriately. The environment should be made as stimulating as possible in case the problem is a reflection of stress and boredom.

 Gabapentin can be used for both pain relief and behavioural modification, given orally at a total dose of 5–35 mg/kg/day (equal divisions administered q8h).

- A multi-drug approach can be used in problematic cases – adding or substituting an opiate, a behavioural modifier such as fluoxetine (Wynchank and Berk, 1998), or a tricyclic antidepressant.
- Topical capsaicin has been used successfully in dogs with atopic dermatitis as an anti-pruritic agent (Marsella et al., 2002).

The author [JS] has had success with topical capsaicin in combination with oral gabapentin (Flecknell and Waterman-Pearson, 2001).

# Care of the respiratory system

Neurological, particularly recumbent, animals are at risk of:

- Hypoventilation
- Aspiration pneumonia
- Pulmonary atelectasis
- · Non-cardiogenic pulmonary oedema.

Any tetraplegic animal is at risk of hypoventilation as a result of paralysis of the muscles of respiration. This paralysis can be a result of LMN (e.g. botulism, polyradiculoneuritis) or UMN (e.g. cervical fracture, atlantoaxial subluxation, brainstem disease) problems.

#### Hypoventilation

This should be suspected in any tetraplegic animal, and the respiratory pattern of all recumbent animals should be checked regularly. If hypoventilation is suspected a blood gas analysis should be obtained; an arterial  $p\mathrm{CO}_2$  >50 mm Hg is concerning and may indicate the need for a ventilator (see Chapter 20). It is also important that the body temperature of tetraplegic animals is monitored and kept within normal range, as hypothermia can exacerbate motor weakness, particularly in animals with LMN problems, and hyperthermia can occur in animals that are unable to pant effectively.

#### Aspiration pneumonia

Animals with megaoesophagus, regurgitation and dysphagia (common with various LMN diseases) are particularly at risk of developing aspiration pneumonia. Aspiration of acidic stomach contents can cause severe pulmonary damage and secondary bacterial pneumonia.

The effect of aspiration can be reduced by decreasing the acidity of stomach contents using H-2 antagonists, such as famotidine (0.5 mg/kg i.v. or orally q12–24h); stomach content acidity should be checked using pH paper on regurgitated stomach contents, and the doses adjusted accordingly. Regurgitation of acidic stomach contents also causes a local oesophagitis that exacerbates megaoesophagus; thus, acid neutralization has a two-fold benefit.

Oesophageal and pharyngeal dysfunction is often apparent (in the form of regurgitation), but can sometimes be difficult to identify. It should be suspected in any animal with LMN disease that swallows repeatedly, drools saliva or coughs after eating or drinking. In animals with megaoesphagus, regurgitation and aspiration can be avoided by placing a naso-oesophageal tube.



- The oesophagus is kept empty by intermittent (every 2–6 hours) aspiration of the naso-oesophageal tube.
- The tube can be left in-situ for only 2–4 days and is not well tolerated by some animals.
- Nothing should be given by mouth to animals that have recently requrgitated.
- If there has been no regurgitation for about 8 hours, a test feeding can be undertaken; the animal should be propped up so that the head is vertically above the stomach. The upright position should be maintained for at least 20 minutes after feeding.
- Some animals manage meatballs best, while others do better with a gruel or more liquid-type food.
- The oesophagus can be aspirated 1 hour later to ensure that the food has passed down to the stomach.
- It is important not to attempt any active exercise for approximately 4 hours after feeding.

#### Pulmonary atelectasis

Prolonged lateral recumbency causes atelectasis of the dependent lung and compromises respiratory function. Whenever possible, animals should be propped into sternal recumbency and their hips flipped from side to side every 4–6 hours, although extremely weak animals may not be able to maintain the sternal position.

Coupage of the entire lung fields should be performed every 4–6 hours as a routine measure in recumbent animals. To do this, the hand is made into a cup and used to percuss the thorax firmly with the aim of making the animal cough (Figure 24.6). This is not possible in some animals immediately after spinal surgery, or in trauma victims, because it can cause pain. In patients with pneumonia, the animal should be nebulized for 5–10 minutes prior to coupage.



24.6 Correct hand position for coupage

When performing hydrotherapy, it is important to remember that the hydrostatic force of water will decrease the patient's lung tidal volume when fully submerged. The increased effort needed to breath against the hydrostatic force will be helpful in cases of pulmonary atelectasis, as it will increase the functional tidal volume. However, caution should be used in patients with serious respiratory compromise, as the additional effort may cause decompensation and have serious respiratory complications. In such patients, hydrotherapy should only be performed under experienced



Hydrotherapy performed with a team approach to ensure that it is both safe and effective.

#### Behaviour

The recovery of neurological patients is greatly influenced by their mental status. Patients that either cannot move or are confined may become bored, the stress of which can cause depression and stereotypical behaviour such as self-mutilation. Added stresses include chronic pain and the inability to complete normal functions such as urination and defecation, eating and drinking.

To a certain extent, the response to injury is influenced by breed and varies with each individual. It is important to know each animal's personality and routine and make their environment compatible with their emotional and physical needs (e.g. some dogs will eat and drink better if they are placed in a sling or cart with elevated bowls).

Knowledge of personality also helps when trying to motivate the animal to perform physiotherapy. Some dogs respond to treats, some love toys and some dogs just have a willingness to please. Mental status should be evaluated daily, and the environment altered or an underlying cause sought if it worsens.

Regular contact with the owner is essential, both for the animal and for the owner so that he/she can learn how to care for the pet appropriately.

#### Nutrition

Adequate nutritional support is a very important aspect of supportive care for neurological patients, as they have undergone significant physiological and psychological stress. (For a full review of nutritional support of hospitalized cats and dogs, see Mauldin and Davidson, 2003.)

### Metabolic response to injury

Nutritional intake is often reduced in neurological patients because they are unable or unwilling to eat, and the metabolic changes that occur are drastically different from those in a healthy fasting dog.

After glycogen stores are depleted, the body does not use fatty acids as the primary energy source but instead relies on protein catabolism. The term coined to describe this condition is 'complicated starvation'. The metabolic response to injury has been divided into three phases:

- The shock phase occurs in conjunction with the injury
- In the *hypermetabolic phase*, the body enters a hypermetabolic state. Increases in metabolic rate and protein catabolism appear to parallel the severity of the illness. During this phase, the clinician must be proactive in order to minimize the loss of lean body mass and provide the nutrients needed for recovery
- The convalescent phase is the time required by the body to replenish its body mass and fat stores, and return to a normal metabolic state.

#### **Energy requirements**

For each patient the daily energy requirements should be calculated and adjustments made based on the response of the patient. Daily maintenance energy requirements can be calculated using the formula:

Resting energy requirement (kcal/day) = 70 x bodyweight<sup>0.75</sup> (kg)

This maintenance value is then multiplied by an 'illness factor' of 1.2 to 1.6. The illness factor is determined by the severity of the illness, the phase of recovery, and assessment of patient weight, body condition and lean body mass. The patient's body

condition is monitored daily and the food intake altered as needed.

The food sources used should be of high density, palatable, nutritionally balanced and have the majority of calories from high quality protein and fat (assuming that the patient does not have a systemic disease that would be complicated by these ingredients). There are several prescription diets on the market that meet these requirements.

#### **Nutritional intake**

The last consideration in nutrition is that the animal actually receives the prescribed nutrients. Feeding by the owner and hand feeding can be extremely beneficial early in the rehabilitation process. If these suggestions fail to produce results, assisted enteral feeding must be employed.

The specific techniques, management and complications of the various methods of assisted feeding are beyond the scope of this chapter but can be found elsewhere (see Further Reading).

Water requirements are estimated to be between 50 and 100 ml/kg of bodyweight per day. Patients that are not eating and drinking on their own should be weighed on the same scales daily to ensure that their hydration status is adequate.

# Physical rehabilitation

When rehabilitating companion animals the needs of both the patient and owner have to be considered. A good functional outcome here depends on both the integrity of the nervous system and the overall health of the patient. Prevention of secondary diseases is much easier than treating them and is an important aspect of rehabilitation. Figure 24.8 summarizes physical therapy techniques used in rehabilitation.

Modality	Indications	Benefits	Contraindications
Range of motion (ROM)	Non-ambulatory; mono, para or tetraparesis; spasticity	Maintains flexibility; maintains integrity of joints, muscles and tendons	Excessive pain; recent surgical repair
Cryotherapy	Recent surgical sites; post- exercise	Pain relief; decreased metabolic demands; decreased haemorrhage/inflammation	Careful use in areas with decreased blood supply
Heat therapy	Subacute/chronic pain; chronic inflammatory conditions; muscle spasm; decreased ROM; excess scar tissue; pre-exercise	Pain relief; increased circulation; decreased inflammation; increased nerve conduction velocity; decreased muscle spasm	Acute inflammation; use with caution in areas with decreased blood supply or patients with circulatory compromise
Massage	Stress/pain; muscle spasm; decreased ROM; recumbency; contractures	Stress/pain relief; decreased muscle spasm; maintenance of tissue perfusion; sensory input to spinal cord	Excessive pain
Interferential electrical stimulation (IES)	Acute and chronic pain; poor circulation; muscle spasm	Pain relief; increased circulation; decreased muscle spasm	Seizures; neoplasia; sepsis; pacemakers; coagulopathies
Active muscle contraction	Paresis (mono, para, hemi or tetraparesis)	Increases muscle strength; counteracts muscle atrophy	Cannot perform if reflex arc is absent (LMN disease)
Neuromuscular electrical stimulation (NMES)	LMN paresis	Increases muscle strength; counteracts muscle atrophy	Some patients will not tolerate; not as effective as active muscle contraction

Modality	Indications	Benefits	Contraindications
Treadmill (land or water)	Paresis (mono, para, hemi or tetraparesis)	Increases muscle strength; counteracts muscle atrophy; increased coordination; controlled environment	Accessibility; manpower needed
Swimming	Paresis (mono, para, hemi or tetraparesis)	Increases muscle strength; counteracts muscle atrophy; increased coordination; water provides weight support, cleans coat	Need appropriate swimming area; urinary tract infection
Proprioceptive training	Paresis (mono, para, hemi or tetraparesis)	Encourages accurate coordination; simple exercises can be done at home	Cannot perform in non-ambulatory animals

24.8 (continued) Physical therapy modalities.

Methods of measuring functional outcomes such as the use of goniometry to measure range of motion (Jaegger *et al.*, 2002), kinematic analysis of gait (McLaughlin, 2001), and expanded gait scoring systems (Olby *et al.*, 2001) facilitate objective evaluation of the benefits of rehabilitation.

#### Range of motion

By definition, range of motion (ROM) techniques is the movement of a joint or body segment through the maximum motion possible (Figure 24.9). This process can be:

- Passive range of movement (PROM) the clinician provides the force needed to drive the motion
- Active range of movement (AROM) the muscles of the patient are responsible for the motion
- Active-assisted range of movement (AAROM) the clinician provides manual assistance during a muscular contraction.

Moving a body segment or joint through its ROM affects:

- Muscles
- Articular cartilage
- Joint capsule
- Ligaments
- Tendons
- Fascia
- Blood vessels
- Nerves.

Immobilization leads to changes in these tissues, some of which can become irreversible if not addressed early in the rehabilitation process. Changes that have been described include: morphological and biochemical changes in articular cartilage; joint capsular and pericapsular contracture; decrease in the thickness and strength of ligaments and tendons (especially at the bone interface); osteoporosis; loss of



Full range of motion in thoracic and pelvic limbs. Note that the digits have also been extended and flexed.

flexibility in muscles, fascia, blood vessels and nerves; and, rarely, myopathic changes (Braund et al., 1980).

PROM is used early in the rehabilitation process to maintain the integrity of the tissues of the body segment involved and to counteract the effects of immobilization. It is also thought that joint movement provides sensory input into the spinal cord, even if the patient does not have voluntary motor function, enhancing establishment of new neural pathways.

Each segment or joint must be taken through its full ROM (to patient tolerance) several times every 8–12 hours. The ROM should be recorded daily so that changes can be documented. This is an exercise that can be completed easily by owners and repeated whenever they are sitting with their pet, as long as they understand not to persist if it appears to be painful for the animal. Contraindications include situations where motion will jeopardize a surgical repair, increase inflammation and/or increase pain.

### **Thermotherapy**

Thermotherapy is defined as the application of heat or cold for the purpose of physical therapy.

### Cryotherapy

This treatment lowers the temperature of the target tissues by transferring heat from the body into the a cooling medium. The degree of cooling is related to the:

- · Temperature of the cooling medium
- · Duration of treatment
- · Vascularization of the treatment area
- Surface area of the target tissue.

This treatment is most commonly delivered via ice packs, ice baths, ice massage and cold compression units.

The local effects of cryotherapy include vasoconstriction and a decrease in cellular metabolism, cell waste, inflammation and pain. These local effects result in pain relief, decreased demand for oxygen, decreased haemorrhage and oedema, and inhibition of degradative enzymes. These properties make cryotherapy the treatment of choice for surgical incisions in the immediate postoperative period, to reduce swelling and pain. It is often helpful to treat the surgical area after the animal has undertaken exercise.

Care must be taken not to overcool an area while treating a patient. The treated areas often have decreased pain sensation and a compromised circulation so the area will cool faster and for longer than normal tissue. The best way to ensure even cooling is to have even contact over the target surface. It is also recommended that a damp towel be placed between ice packs and the skin, and that the duration of cooling is limited to <10–15 minutes. The skin should be monitored intermittently; if it appears cyanotic, or the animal shows discomfort, treatment should be discontinued.

#### Heat therapy

The application of heat to the body can be broken down into *superficial* and *deep* heating.

- Superficial heat is used most commonly in the rehabilitation of companion animals and therefore will be the focus of discussion. It can be employed using simple methods, such as moist heat packs or towels (at 70–75°C (160–170°F)) and warm whirlpools.
- The heating of deep tissue structures (3–5 cm under the skin) is better accomplished with therapeutic ultrasound, set at 1MHz on continuous mode.

The local effects of heat therapy include: vasodilation; an increase in cellular metabolism; extensibility of collagen local blood flow and nerve conduction velocity; and decreased muscle spasm. These properties make heat therapy useful in subacute and chronic phases when the animal is being prepared for therapeutic exercise, to improve the mobility of connective tissues, or provide relief from muscle spasms or pain.

Heat is transferred from the medium to the target tissue. The degree of heating will depend on the:

- Temperature of the heating medium used
- · Time of exposure
- Area of tissue treated
- · Vascularity of the target tissue.

As in cryotherapy, care should be taken in treating areas of reduced vascular supply and innervation to avoid overheating the tissue. In most cases moist hot packs (at 74°C (165°F)) wrapped in a towel can heat target tissues to the desired temperature in 10–15 minutes. Whirlpools and hydrotherapy units should be maintained at 30–37.5°C (90–105°F) to provide effective heating of tissues. Whereas, if the patient is exercising in water the temperature should be maintained closer to 30°C (90°F) to prevent overheating.

Heat therapy is particularly useful in cases where ROM has become a problem, e.g. where scar tissue has become excessive and immobile, in animals with muscle spasm, and in patients that are just starting therapeutic exercise.

#### Massage

Describing all the different types of massage techniques is beyond the scope of this chapter but there are a few strokes that are basic to the delivery of massage (Starkey,1999):

- Effleurage is a technique of stroking or gliding over the muscles with the hands. This technique is usually started with a light touch and gradually intensified as it is continued. It is suggested to follow the pattern of blood flow back to the heart
- Petrissage is a technique that uses a kneading action or pressure and release and is performed on the entire length of muscle groups
- Friction massage is a technique that uses pressure perpendicular to either the muscle fibre direction or scar direction.

If performed correctly the animal should at least tolerate the massage, and ideally will appear to enjoy it.

- The psychological benefits are that massage is enjoyable for the animal, it is relaxing and helps to create a stronger bond between the clinician and patient. These factors all contribute to stress relief.
- The mechanical benefits of massage include: keeping the tissue planes mobile during the recovery process; breaking down adhesions formed by excess scar tissue (using the friction technique); and relieving muscle spasm.
- The reported physiological benefits of massage include sensory input to the nervous system, thereby stimulating the neural pathways, and increasing blood and lymphatic flow, which in turn speeds delivery of nutrients to their target sites and expedites the removal of waste products and inflammatory mediators.

Massage is particularly beneficial in patients that are non-ambulatory, stressed, undergoing neurogenic atrophy, or are in the early stages of therapeutic exercise.

#### Interferential electrical stimulation

Interferential electrical stimulation (IES) is a specific type of stimulation that uses alternating currents on two separate channels (Starkey, 1999). The four electrodes are placed either on the skin or in the sides of a specially designed pool (Figure 24.10) so that the treatment area is within the confines of the electrodes.



A patient in an interferential stimulation unit. The metal strips in the sides of the bath are electrodes (arrowed). The patient is wearing a life jacket for dogs.

When stimulation occurs, mild muscle fasciculations are seen but complete muscle contractions should not occur (unlike neuromuscular electrical stimulation see below).

The purpose of IES is to treat pain, improve the microcirculation and increase cellular metabolism. This technique is particularly useful in the acute postoperative phase and can be used as needed for pain relief. The author [JS] has found that IES can provide up to 24 hours of pain relief in some patients.

Contraindications to this type of therapy include: cancer; infection; coagulopathies; pacemakers; and seizure conditions. Specialized equipment is needed to perform IES, thus patients need to be referred to a dedicated rehabilitation clinic.

# Preserving muscle mass and increasing strength

Preservation of muscle mass is a very difficult aspect of physical rehabilitation in the neurological patient. Upon presentation, some patients have chronic conditions and significant muscle atrophy due to disuse, while dogs that have suffered significant injury (e.g. in road traffic accidents) or have LMN disorders develop rapid and dramatic muscle atrophy. Accurate assessment of the patient will give insight on how best to combat atrophy; for example, providing adequate nutrition in the hypermetabolic phase of recovery following injury may prevent dramatic muscle atrophy.

Active and repetitive muscle contraction by the patient is the best way to maintain and strengthen muscle. Numerous experiments have demonstrated that neuromuscular electrical stimulation (NMES) cannot equal an active voluntary contraction in force, strength or endurance. However, patients that have severe LMN signs do not have intact reflex arcs (at least not at the levels of the lesion) and NMES is the only option for these patients.

#### Active muscle contraction

If the patient has an intact reflex arc, with or without voluntary motor function, active contraction is by far the best way to preserve muscle mass and exercises should be started as soon as possible after injury. Patients can be placed in slings or carts several times a day in a manner that enables them to bear some weight at least for short periods of time (see Figure 24.4). This simple treatment can accomplish many goals:

- Prevention of decubital ulcers
- Prevention of atelectasis
- Positions the animal to eat and observe/interact with surroundings
- Positions the animal so that it can be treated with various modalities using less staff and restraint
- Positions the animal so that a normal posture is maintained, ensuring that the gains made in ROM are not lost
- Partial weight bearing requires active muscle contraction by the weight-bearing muscle groups
- Partial weight bearing stimulates the other connective tissues in the body (i.e. bone, tendons, ligaments, articular cartilage) so that the effects of immobilization are minimized.

The patient can also be submerged in water up to its flank or greater trochanter of the femur, depending on the body style of the patient (Figure 24.11). If there is a surgical incision this can be covered with sterile petroleum jelly to prevent complications in wound healing. Suspension in water will provide support and





A dog working in an underwater treadmill. This dog can now bear weight on its own with the water level coming up to its shoulder, and is completing 15 minutes of exercise.

weight reduction so that exercise will be easier to perform. The goal is to have the limbs in a normal weight-bearing position but only bearing a fraction of the weight. Suspension in water also helps to keep the skin clean (although animals must be dried carefully after the procedure) and the hydrostatic force of the water helps minimize oedema in the extremities and increases tidal volume.

The exercises performed in each patient are determined by its neurological status.

Withdrawal reflexes can be stimulated in animals that lack voluntary motor function. The clinician can provide additional resistance and change the degree of abduction of the limb in order to exercise different muscles as the patient improves. It is beneficial occasionally in paraplegics to exercise non-affected limbs using swimming.

Patients that have regained voluntary motor function have more exercise options:

- Postural reactions can be performed while the patient is supported in either the cart or water
- Creating waves or rocking motions can help stimulate the same sensory and motor pathways as the postural reactions.

In animals where one limb is more severely affected than the others (e.g. brachial plexus avulsion or lateralized LMN signs as a result of fibrocartilaginous embolism (FCE)), the strength of that limb can be increased by lifting the normal limb and forcing weight bearing by the severely affected limb.

As the patient improves, the degree of support provided by either the cart or water is decreased and the duration of exercise is increased. Exercises can be performed to fatigue but as a general rule, if the patient is too tired the following day to perform exercise at the same level, the amount of exercise should be cut back or dropped to every other day until strength and endurance have improved.

#### Neuromuscular electrical stimulation

NMES produces tetanic contraction of muscles viadermal electrodes placed over the muscles to be worked. This treatment is indicated in animals that cannot produce active contractions of muscles (i.e. LMN paralysis) and helps to slow neurogenic muscle atrophy. There are several types of unit on the market (Figure 24.12). Each unit has several different parameters, some of which can be adjusted. The authors' advice is to buy a unit that allows changes to the stimulation parameters in order to give greater flexibility in treatment. A unit that has multiple channels is also beneficial as, several muscle groups can be contracted simultaneously during the treatment, thus allowing co-contraction or alternating contraction of muscle groups.



24.12 A neuromuscular electrical stimulation (NMES) unit with carbon rubber electrodes attached.

The parameters that need to be considered include:

- Type of current monophasic (DC), biphasic (AC), polyphasic (Russian). There is no demonstrated benefit of one current over another, but some animals will only tolerate one particular current
- Frequency rate of oscillations in cycles per second (PPS)
- Phase/pulse duration the length of time of a single phase or pulse (microseconds)
- Waveform the visual shape of the waveform on a graph
- Amplitude the intensity of the delivered pulse
- On/off time the length of time the stimulator is on compared with the length of rest time between contractions; can be given as a ratio (i.e. 1:5 = 10 seconds on and 50 seconds off)
- Ramp the time that the machine takes to go from 0 to the set amplitude
- Polarity anode or cathode.

When the treatment is being administered, the clinician needs to consider the following points:

- The hair (over the muscle groups to be stimulated) should be clipped and the skin cleaned
- The largest size electrodes that will fit on the muscle to be stimulated should be used – carbon rubber electrodes are excellent because they can be trimmed easily and reused
- Ultrasound gel can be used as a conduction medium
- An electrode should be placed at the origin and insertion of the muscle to be stimulated and moved around at a low setting to find the motor point of the muscle (area of best contraction; usually in the proximal third of the muscle)
- The muscles can be stimulated once a day for up to 15 minutes until the animal is able to produce an active contraction
- Some patients do not tolerate NMES and some will tolerate it only with sedation
- Handlers should always use caution with the patient, especially the first time this modality is used, as it is an unusual sensation for the animal.

A suggested protocol for NMES treatment is given in Figure 24.13.

#### Suggested protocol

- Start with an on/off time of 1:3 and work up to a 1:2
- Use a frequency between 30–50 PPS and a ramp time of 2–3 seconds
- Amplitude is set to patient tolerance with the goal of obtaining good muscle contraction

24.13

A suggested protocol for neuromuscular electrical stimulation (NMES) treatment.

#### Gait training

This term describes the methods used to encourage normal ambulation using the affected limbs correctly in a straight line at different speeds. Equipment needed to perform this type of exercise is dependent upon the neurological status of the patient.

- If the patient has no voluntary motor function it can be placed in an underwater treadmill at standing height (see Figure 24.11).
- The treadmill is started at a slow walking speed and the veterinary surgeon (who is in the tank with the patient) stimulates the withdrawal reflex by pinching over the bones of the digit and then the extensor reflex by digital stimulation of the plantar/palmar aspect of the paw, in each limb to produce stepping movements.

This process does take a little practice but is not hard to learn. The same exercise can be accomplished with a cart for support and a human land treadmill. The patient's paws should be protected (see Figure 24.4) from the non-slip surface on the

treadmill. This exercise can be performed for 5–10 minutes twice daily. As the patient begins to regain voluntary motor function, or in some cases learns to walk reflexively, the muscle groups will start to contract without external stimulation. At this point, assistance should be provided for correct movement and placement of the affected limbs.

As the patient progresses and the need for assistance decreases, the speed of the treadmill and the duration of the exercises can slowly be increased. Correct placement of paws and limb coordination should be maintained all the time to ensure that the patient does not develop 'bad habits' (e.g. 'bunny hopping' with both hindlimbs together).

Once a fast walk is reached, the amount of support provided by the cart or water can be decreased while decreasing the speed of the treadmill. Again, correct cadence to the walk should be encouraged. The patient should not be allowed to trot, pace or gallop until late in the rehabilitative process (i.e. well advanced in the proprioceptive neuromuscular training). Animals are masters at compensation and 'bad habits' are easy to develop and hard to correct.

Hydrotherapy in the form of swimming can be a very effective means of enhancing strength and coordination in the recovering dog. In general, this is started between 7 and 14 days after surgery to allow time for the incision to heal. Life jackets for dogs can be purchased to provide extra support (see Figure 24.10) and owners can swim their dogs either in the bathtub (if a small animal) or in a swimming pool, lake or even the sea.

- When starting in the bathtub, the patient should be able to touch the bottom at first before progressing to swimming.
- The patient can be encouraged to swim the length of the tub by offering treats or playing with a ball.
- As for other exercises, the duration of swimming is dictated by each animal.
- When the animal appears fatigued, the exercise should be discontinued (and, as previously stated, if they are unable to perform to the same level the next day, the duration of exercise should be shortened or taken to every other day until endurance has improved).

It is important that owners only attempt to place their pet in water if they have the capability to get the animal in and out of the water safely, thus large non-ambulatory dogs need to undergo therapy at a specialized facility where adequate slings and lifts are available (Figure 24.14).

#### Proprioceptive neuromuscular training

This term describes the exercises used to enhance the patient's awareness and use of its limbs at rest and in motion (Figure 24.15). Typically, patients will not start these exercises until they are able to bear a significant portion of weight and can walk with some assistance. The author [JS] has had success introducing exercises in the following order:



## 24.14

A mechanical hoist enables movement of large patients into and out of bathing facilities.

- 1. Balance of weight in a stationary position
- Balance of weight in a stationary position with methods used to throw patient off balance (i.e. wobble board, physical pressure, waves, closed cell foam mat on top of water)
- 3. Patient lifting limbs over obstacles while walking in a straight line (height of obstacles and distance between them can be increased and decreased, respectively, as patient progresses)
- Off-balance walking patient walks in straight line while clinician throws patient off balance using pressure or theraband sling
- 5. Weaving in and out of cones start with a distance between the cones at least equal to the distance between the thoracic and pelvic limbs (as the patient improves decrease the distance

- between the cones)
- Patient lifting limbs over obstacles in a circular fashion (similar to a wagon wheel) – start with 4–6 objects; make sure the patient performs the exercise in both clockwise and anticlockwise directions
- 7. Patient performs previously mentioned drills with increased stimulation on affected limbs (i.e. boots, band around the ankle)
- Patient performs above exercises after a level of fatigue is reached with another type of exercise.

The aim of these exercises is to enhance the correct paw placement and coordination. Many of these exercises can be supervised at home by the owner if they are shown what to do.

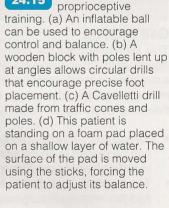
#### Conclusion

Devising an appropriate plan for rehabilitation is a critical component of treating patients recovering from or with ongoing, neurological disease. Animals with severe injuries (i.e. non-ambulatory animals) will greatly benefit from rehabilitation at a dedicated centre where their general management can be achieved more easily and they can benefit from the use of specialist equipment, such as underwater treadmills. However, exercises such as PROM, cone drills and swimming can be completed with the help of the owner at home without difficulty. Appropriate care of the animal's overall health and well-being will improve the response to therapy and it is important to understand that the rehabilitative process should start immediately after injury or surgery.

24.15







Equipment to aid in





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# **Appendix 1**

# Neurological disorders associated with cat and dog breeds

Carley J. Abramson

This section lists neurological disorders that are likely to be encountered in practice. Some of these have proven modes of inheritance in a breed, others have a breed over-representation, and some have been reported in the breed but the exact prevalence is still unknown. Many of these disorders are 'diagnosed' only by elimination of other causes of neurological dysfunction or via post-mortem pathology; however,

the diagnostic aids listed are tools that may assist in confirming a suspected disorder. Though every effort has been made to offer as much clinically useful information as possible, there can be no guarantee that this is a complete list of breed-related diseases at the time of publication. Figures A1.1 and A1.2 detail the idiopathic, inherited and breed associated diseases in cats and dogs.

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
Abyssinian	Myasthenia gravis	Generalized weakness	Anti-ACh receptor antibody; electrodiagnostics; tensilon test
Birman	Distal central-peripheral axonopathy	8–10 months; hypermetria; progressive paraparesis; plantigrade stance	Nerve biopsy
	Spongiform encephalopathy	7 weeks; hypermetria; paraparesis; depression	Pathology
Burmese	Hypokalaemia	2–6 months; intermittent muscle weakness; ventroflexion of neck	Hypokalaemia; elevated CK
	Congenital vestibular disease	Birth to 4 months; head tilt; ataxia; circling	Clinical signs; exclusion diagnosis; pathology
Devon Rex	Hereditary myopathy	1–6 months; muscle atrophy; megaoesophagus; cervical ventroflexion; progressive tetraparesis	Muscle biopsy
Domestic Short-	Neuroaxonal dystrophy	5–6 weeks; head tremors; ataxia; hypermetria	Pathology
hair	X-linked (hypertrophic) muscular dystrophy	5–6 months; skeletal muscle hypertrophy; exercise intolerance; regurgitation; tongue protrusion; hypertrophic cardiomyopathy	Elevated CK; EMG abnormalities; pathology
Egyptian Mau	Spongiform encephalopathy	7 weeks; hypermetria; paraparesis; depression	Pathology
Korat	Lissencephaly	Within 12 months; depression; behaviour change; seizures	Imaging (CT, MRI); pathology
Manx	Spina bifida/sacrocaudal dysgenesis	4 weeks to months; paraparesis; urinary and faecal incontinence; hypoalgesia in the pelvic limbs	Imaging (radiography, myelography, CT, MRI); pathology
Siamese	Congenital vestibular disease and deafness	Birth to 4 months; head tilt; ataxia; circling; deafness	Clinical signs; exclusion diagnosis; BAER; pathology
Tonkanese	Congenital vestibular disease	Birth to 4 months; head tilt; ataxia; circling	Clinical signs; exclusion diagnosis; pathology

Idiopathic, inherited or breed associated diseases in cats. ACh = acetylcholine; BAER = brainstem auditory evoked response; CK = creatine kinase; CT = computed tomography; EMG = electromyography; MRI = magnetic resonance imaging.

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
Afghan Hound	Hereditary myelopathy	3–13 months; paraparesis; ataxia. Progressive to tetraparesis & death from respiratory failure	Clinical signs; pathology
Airedale Terrier	Cerebellar degeneration	12 weeks; cerebellar syndrome	Pathology

**Appendix 1** Neurological disorders associated with cat and dog breeds

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
kita	Cerebellar degeneration	Cerebellar syndrome	Pathology
	Congenital vestibular disease	Up to 4 weeks; head tilt; circling; ataxia	Clinical signs
	Myasthenia gravis	Generalized weakness; megaoesophagus; laryngeal paralysis	Clinical signs; tensilon test; anti-ACh receptor antibody; electrodiagnostics; muscle biopsy
Alaskan Husky	Necrotizing encephalopathy (Leigh's disease)	7 months–3 years; ataxia; seizures; behaviour changes; may stabilize with intermittent gait disorder and seizures	Pathology
Alaskan Malamute	Peripheral neuropathy	7–18 months; progressive tetraparesis; poor reflexes; muscle atrophy	Electrodiagnostics; nerve and muscle biopsy
American Staffordshire errier	Cerebellar cortical degeneration	2–8 years; progressive cerebellar and vestibular signs	Pathology; cerebellar atrophy on MRI
Australian Cattle Dog	Polioencephalomyelopathy	Within 12 months; seizures followed by fatigue and progressive spastic tetraparesis	Pathology
Australian Kelpie	Cerebellar cortical degeneration	6–12 weeks; cerebellar syndrome; proprioceptive deficits	Pathology
Basset Hound	Cervical spondylomyelopathy	Progressive tetraparesis; neck pain	Imaging (CT, MRI, myelography)
Beagle	Congenital vestibular disease	Up to 4 weeks; head tilt; circling; ataxia	Clinical signs; exclusion diagnosis
	Cerebellar cortical degeneration	3 weeks; cerebellar syndrome	Pathology
	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	Steroid-responsive meningitis-arteritis	<12 months; recurrent fever and neck pain	Clinical signs; CSF neutrophilic pleocytosis; serum and CSF IgA levels <sup>a</sup>
Belgian Tervueren	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	Muscular dystrophy	6 weeks; stiff gait; stunted growth; muscle atrophy	Elevated CK; muscle biopsy
Bernese Mountain Dog	Dysmyelination	2–8 weeks; fine tremor of head and limbs; weakness; stiffness; may improve with age	Clinical signs; pathology
	Steroid-responsive meningitis-arteritis	<12 months; recurrent fever and neck pain	Clinical signs; CSF neutrophilic pleocytosis Serum and CSF IgA levels <sup>a</sup>
	Hepatocerebellar disease	4–6 weeks; progressive wide-based stance; spontaneous nystagmus; head bobbing; paresis	Raised bile acids; ammonia; pathology
Border Collie	Cerebellar cortical degeneration	6–8 weeks; cerebellar syndrome	Clinical signs; pathology
	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	Deafness	6–8 weeks	BAER
	Peripheral sensory neuropathy	2–6 months; progressive ataxia; gait abnormality in all limbs with preservation of strength; self-mutilation	Clinical signs confirming sensory loss in limbs electrodiagnostics; nerve biopsy
Borzoi	Cervical malformation (Wobbler syndrome)	Progressive tetraparesis; neck pain	Imaging (CT, MRI, myelography)
Boston Terrier	Hydrocephalus	Cerebral signs (seizures, depression)	Imaging (ultrasonography, CT, MRI)
	Hemivertebrae	Ataxia; spinal curvature; incontinence; paresis	Imaging (radiography, CT, MRI)
Bouvier des Flandres	Idiopathic laryngeal paralysis	4–6 months; inspiratory stridor; voice change; dyspnoea	Electrodiagnostics, laryngoscopy
	Myopathy	Within 2 years; generalized muscle weakness and atrophy; dysphagia; degeneration of pharyngeal and oesophageal muscles leads to regurgitation	Elevated CK; electrodiagnostics; muscle biop
Boxer	Progressive axonopathy	2 months; progressive ataxia and weakness; diminished proprioception, muscle tone, patellar reflexes; intact pain sensation	Electrodiagnostics; nerve biopsy; pathology
	Steroid-responsive meningitis-arteritis	<12 months; recurrent fever and neck pain	Clinical signs; CSF neutrophilic pleocytosis; serum and CSF IgA levels <sup>a</sup>
	Immune-mediated polymyositis	Generalized muscle weakness; myalgia; possible dysphagia and/or megaoesophagus; muscle atrophy	Elevated CK; electrodiagnostics; muscle biop

# **Appendix 1** Neurological disorders associated with cat and dog breeds

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
Brittany Spaniel	Cerebellar degeneration	7–13 years; progressive spasticity; hypermetria and truncal ataxia	Pathology
	Spinal muscular atrophy (motor neuron disease)	Weakness; atrophy of proximal muscles. Accelerated form: 6–8 weeks, immobile by 3–4 months; intermediate form: 6–12 months, immobile by 3 years; chronic form: survive into adulthood	Clinical signs; EMG abnormalities; pathology
Bullmastiff	Cerebellar degeneration	4–9 weeks; ataxia; hypermetria; intention tremor	Pathology
	Spongiosis of grey matter	6–9 weeks; ataxia; hypermetria; intention tremor; slow menace; visual deficits; poor proprioception	Pathology
Bull Terrier	Cerebellar degeneration	Cerebellar syndrome	Pathology
	Idiopathic laryngeal paralysis	Stridor; exercise intolerance	EMG abnormalities; laryngoscopy
Cairn Terrier	Cerebellar degeneration	Cerebellar syndrome	Pathology
	Multisystem neuronal degeneration	4–7 months; progressive tetraparesis; cataplexy; cerebellar dysfunction	Pathology
Cavalier King Charles Spaniel	Episodic hypertonicity	3–4 months; pelvic limb stiffness/collapse after exercise or stress; no loss of consciousness; progressive	Clinical signs; exclusion diagnosis
	Chiari-like malformation (caudal occipital malformation syndrome)	Often has accompanying hydrocephalus and syringohydromyelia; seizures; depression; ataxia; cerebellar syndrome; vestibular signs; other signs of syringohydromyelia (see below)	Imaging (MRI)
	Syringohydromyelia	Ataxia; depressed reflexes if in spinal cord intumescence; spinal curvature; paraesthesia of paraspinal dermal zone	Imaging (MRI)
Chihuahua	Hydrocephalus	Cerebral signs (seizures, depression)	Imaging (ultrasonography, CT, MRI)
Chow Chow	Dysmyelination	2–4 weeks; intention tremors; dysmetria 'bunny-hopping'; improves after 1 year	Clinical signs; pathology
	Myotonia congenita	2–3 months; stiffness after rest that improves with exercise; possible dyspnoea	Clinical signs; EMG abnormalities; muscle biops
	Cerebellar hypoplasia	Cerebellar syndrome	Pathology
Cocker Spaniel	Congenital vestibular disease	Head tilt; ataxia; circling	Clinical signs
	Neuronal degeneration	10–14 months; behaviour and personality change; absent menace; variable hypermetria and falling	Pathology
Collies (smooth and rough-coated)	Dermatomyositis	2-6 months; inflammation of muscle, skin, blood vessels; cyclical and self-limiting	Muscle and skin biopsy; EMG abnormalities
	Cerebellar cortical degeneration	1–2 months; cerebellar syndrome may stabilize by 12 months	Pathology
	Neuroaxonal dystrophy	2-4 months; hypermetria; ataxia; intention tremor	Clinical signs; pathology
Coton de Tulear Dog	Neonatal cerebellar ataxia	2 weeks; ataxia; 'swimming' movements (unable to stand); ocular saccadic dysmetria; head titubation; non-progressive until at least 4 months	Ultrastructural (electron microscopy) pathology
	Cerebellar degeneration	2–3 months; cerebellar syndrome	Pathology
Cretan Hound	Spongiform leucoencephalopathy (hypomyelination/'shaker' pup)	2–3 weeks; generalized tremors worse with excitement	Pathology
Dachshund	Narcolepsy-cataplexy	Sudden flaccid paralysis ± loss of consciousness	Clinical signs; DNA test <sup>b</sup>
	Sensory neuropathy	Progressive loss of spinal reflexes; self-mutilation	Clinical signs; nerve biopsy
	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	Congenital myasthenia gravis	5–6 weeks; progressive episodic weakness resolves with age	Tensilon test; electrodiagnostics; muscle biopsy

# **Appendix 1** Neurological disorders associated with cat and dog breeds

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
Dalmation	Laryngeal paralysis-polyneuropathy complex	4–6 months; inspiratory stridor; voice change; dyspnoea; generalized weakness; megaoesphagus	Electrodiagnostics; laryngoscopy; pathology
	Cerebral and spinal leucodystrophy	3–6 months; visual deficits; progressive ataxia and weakness	Pathology
	Congenital deafness	6–8 weeks	BAER
Dobermann	Narcolepsy-cataplexy	Sudden flaccid paralysis ± loss of consciousness	Clinical signs; DNA test b
Pinscner	Dancing Dobermann disease (neuropathy/myopathy)	6 months-7 years; progressive intermittent flexion of one, then both pelvic limbs	Clinical signs; muscle and nerve biopsy; EMG (esp. gastrocnemius)
	Cervical spondylomyelopathy (Wobbler syndrome)	>5 years; progressive tetraparesis ± neck pain	Imaging (CT, MRI, myelography)
	Congenital vestibular disease and deafness	Up to 4 weeks; head tilt; circling; ataxia; deafness	Clinical signs
English Bulldog	Cerebellar cortical abiotrophy	2 months; progressive cerebellar syndrome	Pathology
	Spina bifida	4 weeks to months; paraparesis; urinary and faecal incontinence; hypoalgesia in the pelvic limbs	Imaging (radiography, myelography, CT, MRI); pathology
	Hemivertebrae	Ataxia; spine curvature; incontinence	Imaging (radiography, CT, MRI)
English Pointer	Spinal muscular atrophy (motor neuron disease)	5 months; weakness; dysphonia; loss of spinal reflexes; progressive muscle atrophy over 3–4 months	Clinical signs; electrodiagnostics; nerve biopsy; pathology
	Sensory neuropathy	Loss of spinal reflexes with preservation of muscle strength; ataxia; hypoalgesia; self-mutilation	Clinical signs; nerve biopsy
Finnish Harrier	Cerebellar degeneration	Cerebellar syndrome	Pathology
French Bulldog	Hemivertebrae	Ataxia; spine curvature; incontinence	Imaging (radiography, CT, MRI)
Gammel Dansk Honschund	Congenital myasthenia gravis (presynaptic)	Progressive episodic weakness	Tensilon test; electrodiagnostics; muscle biopsy
German	Congenital vestibular disease	3 months; head tilt; ataxia	Exclusion diagnosis
Shepherd Dog	Giant axonal neuropathy	14–16 months; progressive paresis; decreased proprioception; poor muscle tone; atrophy of distal limb muscles	Clinical signs; electrodiagnostics; nerve biopsy
	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	Fibrotic myopathy	2–7 years; non-painful lameness in pelvic limb; palpable fibrous band in semitendinous muscle	Clinical signs; electrodiagnostics; muscle biops
	Megaoesophagus	From birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
	Degenerative myelopathy	>5 years (younger reported); progressive paraparesis	Exclusion diagnosis; pathology
	Myasthenia gravis	Generalized weakness; megaoesophagus; laryngeal paralysis	Clinical signs; tensilon test; anti-ACh receptor antibody; electrodiagnostics
	Immune-mediated polymyositis	Generalized muscle weakness; myalgia; possible dysphagia and/or megaoesophagus; muscle atrophy	Elevated CK; electrodiagnostics; muscle biopsy
German Shorthaired	Steroid-responsive meningitis–arteritis	<12 months; recurrent fever and neck pain	Clinical signs; CSF neutrophilic pleocytosis; serum and CSF IgA levels <sup>a</sup>
Pointer	X-linked muscular dystrophy	<12 weeks; stunted growth, stiff/stilted gait; exercise intolerance; muscle atrophy and contractures; pharyngeaf/laryngeal dysfunction	Elevated CK, electrodiagnostics, muscle biops
Golden Retriever	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	X-linked muscular dystrophy	6–9 weeks; stunted growth; stiff/stilted gait; exercise intolerance; muscle atrophy and contractures; pharyngeal/laryngeal dysfunction	Elevated CK; electrodiagnostics; muscle biops
	Myasthenia gravis	Generalized weakness; megaoesophagus; laryngeal paralysis	Clinical signs; tensilon test; anti-ACh receptor antibody; electrodiagnostics

**Appendix 1** Neurological disorders associated with cat and dog breeds

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
Gordon Setter	Cerebellar cortical degeneration	6–30 months; slow progressive cerebellar and vestibular signs	Pathology
Great Dane	Myotonic myopathy	2–3 months; stiffness after rest that resolves with exercise; possible dyspnoea	Clinical signs; EMG abnormalities; muscle biops
	Cervical spondylomyelopathy (Wobbler syndrome)	<2 years; progressive tetraparesis ± neck pain	Imaging (CT, MRI, myelography)
	Megaoesophagus	From birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
	Distal symmetrical polyneuropathy	1–5 years; paraparesis progressing to tetraparesis	Electrodiagnostics; nerve biopsy
	Core-like myopathy	6 months; generalized weakness; exercise intolerance; mild proximal muscle atrophy	Electrodiagnostics; muscle biopsy
Greyhound	Megaoesophagus	Birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
	Steroid-responsive meningitis-arteritis	<12 months; recurrent fever and neck pain	Clinical signs; CSF neutrophilic pleocytosis; serum and CSF IgA levels <sup>a</sup>
Irish Setter	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	Lissencephaly	Within 12 months; depression; behaviour change; seizures	Imaging (CT, MRI); pathology
	Megaoesophagus	From birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
	Cerebellar dysplasia	Cerebellar syndrome	Pathology
Irish Terrier	Muscular dystrophy	6 weeks; stiff gait; stunted growth; muscle atrophy	Elevated CK; muscle biopsy
Italian Spinone	Cerebellar/cortical degeneration	Adult onset; progressive cerebellar signs (UK)	Pathology
Jack Russell	Congenital myasthenia gravis	6-9 weeks; progressive episodic weakness	Tensilon test; electrodiagnostics; muscle biopsy
Terrier (Parson Russell Terrier)	Spinocerebellar degeneration/ hereditary ataxia	2-6 months; cerebellar ataxia; progressive dysmetria and spasticity; intention tremor	Pathology
Japanese Spitz	Muscular dystrophy	10–12 weeks; excessive salivation and dysphagia; progressive exercise intolerance; myalgia	Elevated CK; muscle biopsy
Keeshond	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
Kerry Blue Terrier	Cerebellar cortical degeneration	8–16 weeks; pelvic limb stiffness and head tremors; then dysmetria	Pathology
Kooiker Hound (Dutch Decoy Dog)	Hereditary necrotizing myelopathy	3–12 months; hindlimb paresis; possible urinary incontinence	Pathology
Labrador	Narcolepsy-cataplexy	Sudden flaccid paralysis ± loss of consciousness	Clinical signs; DNA test <sup>b</sup>
Retriever	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
	Exercise-induced collapse	7 months–2 years; mostly field-trial breedings; weakness at collapse after strenuous exercise; requires 10–20 minutes to recover; may be fatal	Clinical signs; exclusion diagnosis
	Familial myopathy	6 weeks–7 months; recessive inheritance; stiff gait; 'bunny-hopping'; cervical ventroflexion; depressed spinal reflexes; stabilizes by 8–12 months	Clinical signs; muscle biopsy
	Familial reflex myoclonus	3 weeks; intermittent muscle spasms; progressive stiffness	Clinical signs
	Cerebellar cortical degeneration	12 weeks; cerebellar syndrome	Pathology
	Axonopathy	From birth; crouched; short-strided gait; thoracic limb hypermetria; unable to stand by 5 months	Clinical signs; electrodiagnostics; nerve biopsy; pathology
Leonberger	Polyneuropathy	1–2 years; progressive tetraparesis; muscle atrophy; decreased spinal reflexes; dysphonia	Clinical signs; electrophysiology; muscle and nerve biopsy

**Appendix 1** Neurological disorders associated with cat and dog breeds

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
Lhasa Apso	Lissencephaly	Within 12 months; depression; behaviour change; seizures	Imaging (CT, MRI); pathology
Maltese	Shaker dog/idiopathic tremors	9 months-2 years; generalized tremors; mild hypermetria	Clinical signs; exclusion diagnosis; treatment response
	Necrotizing encephalitis	6 months-7 years; seizures; depression; circling; head pressing; central blindness	Signalment; CSF; imaging (MRI or CT); pathology
Miniature	Myotonia congenita	Muscular stiffness; possible dyspnoea	Clinical signs; EMG; pathology; DNA test b
Schnauzer	Megaoesophagus	From birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
Newfoundland	Megaoesophagus	From birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
	Immune-mediated polymyositis	Generalized muscle weakness; myalgia; possible dysphagia and/or megaoesphagus; muscle atrophy	Elevated CK; electrodiagnostics; muscle biopsy
Old English	Cerebellar cortical abiotrophy	Progressive cerebellar syndrome	Clinical signs; pathology
Sheepdog	Muscular dystrophy	6 weeks; stiff gait; stunted growth; muscle atrophy	Elevated CK; electrodiagnostics; muscle biopsy
Papillon	Neuroaxonal dystrophy (only one litter reported)	14 weeks; rapidly progressive ataxia and hypermetria; decreased postural reactions	Pathology
Pembroke Welsh Corgi	Degenerative myelopathy	>5 years; progressive paraparesis	Exclusion diagnosis; pathology
Pomeranian	Hydrocephalus	Cerebral signs (depression, seizures)	Imaging (ultrasonography, CT, MRI)
Poodle	Narcolepsy-cataplexy	Sudden flaccid paralysis without loss of consciousness	Clinical signs; exclusion diagnosis; CSF hypocretin levels
	Idiopathic epilepsy (Standard Poodle)	Up to 6 years; seizures	Exclusion diagnosis
	Cerebellar and cerebral degeneration	Soon after birth; cerebellar syndrome	Clinical signs; pathology
Pug	Necrotizing meningoencephalomyelitis	6 months-7 years; seizures; depression; circling; head pressing; central blindness	Signalment; CSF; imaging (MRI or CT); pathology
	Hemivertebrae	Ataxia; spine curvature; incontinence	Imaging (radiography, CT, MRI)
Pyrenean Mountain Dog	Laryngeal paralysis–polyneuropathy complex	4–6 months; inspiratory stridor; voice change; dyspnoea; generalized weakness; megaoesophagus	Electrodiagnostics; laryngoscopy; pathology
Rhodesian Ridgeback	Cerebellar cortical abiotrophy and colour dilution	2 weeks; ataxia; lateral recumbency; opisthotonus; poor growth; affected pups have light hair coat and blue irises at birth	Pathology
Rottweiler	Progressive polyneuropathy	Adult onset; progressive tetraparesis; hyporeflexia; hypotonia; appendicular muscle atrophy	Electrodiagnostics; nerve biopsy
	Spinal muscular atrophy/motor neuron disease	4 weeks; pelvic limb ataxia progressing to tetraparesis	Clinical signs; EMG abnormalities; pathology
	Muscular dystrophy	6 weeks; stiff gait; stunted growth; muscle atrophy	Elevated CK; electrodiagnostics; muscle biops
	Spongiosis of grey matter	6–16 weeks; progressive ataxia and dysmetria; some behaviour change; laryngeal paralysis; microphthalmia	Imaging (MRI); pathology
	Leucoencephalomyelopathy	1–4 years; ataxia; tetraparesis; hypermetria; increased muscle tone/spinal reflexes; often more severe in thoracic limbs	Clinical signs; pathology
	Neuroaxonal dystrophy	Within 12 months; slowly progressive ataxia; hypermetria; wide-based stance; eventually intention tremors and nystagmus	Clinical signs; pathology
	Distal myopathy	Begins at time pup starts walking; plantigrade/ palmigrade stance; hypotonia; poor muscle mass	EMG abnormalities; muscle biopsy (distal)
	Spinal subarachnoid (pseudo) cyst	Progressive ataxia; often ambulatory tetraparesis	Imaging (myelography, CT, MRI); surgical pathology
	Laryngeal paralysis–polyneuropathy complex	4–6 months; inspiratory stridor; voice change; dyspnoea; generalized weakness; megaoesophagus	Electrodiagnostics; laryngoscopy; pathology

**Appendix 1** Neurological disorders associated with cat and dog breeds

Breed	Disease	Clinical signs (including age of onset where known)	Diagnostic aids
Saint Bernard	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
Saluki	Spongiosis of grey matter	Behaviour changes; seizures; aimless wandering	Imaging (MRI); pathology
Samoyed	Hypomyelination	3 weeks; generalized tremors; nystagmus; absent menace	Clinical signs; pathology
	Lissencephaly	Within 12 months; depression; behaviour change; seizures	Imaging (CT, MRI); pathology
	Cerebellar cortical abiotrophy	Cerebellar syndrome	Pathology
	Muscular dystrophy	6 weeks; stiff gait; stunted growth; muscle atrophy	Elevated CK; muscle biopsy
Scottish Terrier	Scotty cramp (spinal serotonin disorder)	Mostly <6 months at onset; progressive stiffness to collapse upon exercise	Clinical signs; methysergide test
	Cerebellar cortical abiotrophy	2-8 years; progressive cerebellar and vestibular signs	Pathology; cerebellar atrophy on MRI
Shar Pei	Megaoesophagus	From birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
Shetland Sheepdog	Dermatomyositis	2–6 months; inflammation of muscle, skin, blood vessels; cyclical and self-limiting	Muscle and skin biopsy; EMG abnormalities
	Dysmyelination	1–3 weeks; seizure; depression; lateral recumbency; intention tremors	Pathology
Siberian Husky	Laryngeal paralysis	4-6 months; inspiratory stridor; voice change; dyspnoea	EMG abnormalities; laryngoscopy; pathology
	Degenerative myelopathy	Progressive paraparesis	Exclusion diagnosis; pathology
Smooth-haired Fox Terrier	Congenital myasthenia gravis	6-9 weeks; progressive episodic weakness; megaoesophagus	Tensilon test; electrodiagnostics; muscle biopsy
	Congenital vestibular disease	3 months; head tilt; ataxia	Exclusion diagnosis
Springer Spaniel	Congenital myasthenia gravis	6–9 weeks; progressive episodic weakness	Tensilon test; electrodiagnostics; muscle biopsy
	Dysmyelination	2–4 weeks; severe tremors; difficulty standing; seizures; progressive debilitation	Pathology
Staffordshire Bull Terrier	Myotonic myopathy	2–3 months; stiffness after rest that resolves with exercise; possible dyspnoea	Clinical signs; EMG abnormalities; muscle biopsy
Swedish Lapland Dog	Spinal muscular atrophy/multisystem neuronal abiotrophy	5–7 weeks; progressive tetraparesis; muscle wasting and deformation (distal limbs); loss of spinal reflexes	Clinical signs; EMG abnormalities; pathology
Tibetan Mastiff	Hypertrophic neuropathy	7-10 weeks; generalized weakness; poor reflexes; dysphonia; normal pain perception; may be recumbent within 3-4 weeks; muscle atrophy	Clinical signs; electrodiagnostics; nerve biopsy
Viszla	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
Weimaraner	Hypomyelination	3 weeks; generalized tremor; dysmetria; several dogs normal by 12 months	Clinical signs; pathology
	Steroid-responsive meningitis-arteritis	<12 months; recurrent fever and neck pain	Clinical signs; CSF neutrophilic pleocytosis; serum and CSF IgA levels <sup>a</sup>
West Highland White Terrier	Shaker dog/idiopathic tremors	9 months–2 years; generalized tremors; mild hypermetria	Clinical signs; treatment response
Wire-haired Fox	Idiopathic epilepsy	Up to 6 years; seizures	Exclusion diagnosis
Terrier	Lissencephaly	Within 12 months; depression; behaviour change; seizures	Imaging (CT, MRI); pathology
	Cerebellar hypoplasia	Birth; cerebellar syndrome	Imaging (CT, MRI); pathology
	Megaoesophagus	Birth; regurgitation	Clinical signs; imaging (radiography, oesophagram)
Yorkshire Terrier	Necrotizing encephalitis	Seizures; motor dysfunction; mental disorientation	CSF; imaging (MRI, CT); pathology
	Necrotizing encephalopathy (Leigh's disease)	4–12 months; seizures; progressive ataxia and dysmetria; central blindness; cranial nerve deficits	Imaging (CT, MRI); pathology; ultrastructural (electron microscopy) pathology

#### Inborn errors of metabolism

This section contains information on inborn errors of metabolism that affect the central nervous system in dogs and cats. These include storage diseases (metabolic errors that lead to a build-up of an intermediate product within the cell, see Chapters 8 and 12), and non-storage diseases, where there is no gross accumulation of material within a cell but the lack of final product or toxic levels of intermediate product leads to malfunction of the cell.

These diseases all share the pathology of a meta-

bolic enzyme abnormality, which is inherited – usually (but not always) as an autosomal recessive disorder. There are several laboratories that will screen for these disorders, either via DNA confirmation or metabolite analysis of tissues or body fluids (e.g. urine or blood). A listing of laboratories that currently offer these commercial services is given at the end of this section. Though every effort has been made to offer as much clinically useful information as possible, there can be no guarantee that this is a complete list of diseases, breed associations and laboratory services at the time of publication.

Breed	Disease	Clinical signs (including age of onset where known)	Diagnosis
Balinese	Niemann-Pick type A	Cerebellar/vestibular signs; depression; peripheral neuropathy	Enzyme assay in leucocytes and/or cultured fibroblasts
Domestic	Mannosidosis	<6 months at onset; connective tissue and skeletal malformation; possible peripheral nerve pathology	DNA testing <sup>a</sup>
	GM, gangliosidosis	Young animals show cerebellar signs; may have dwarfism and facial dysmorphism	Oligosaccharide urinalysis ab; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
	GM <sub>2</sub> gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide urinalysis ab; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
	Globoid cell leucodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis; cerebral signs later; may have peripheral neuropathy	DNA testing °; peripheral nerve biopsy is suggestive of diagnosis; enzyme assay in leucocytes; cultured fibroblasts
	Niemann-Pick type C	Ataxia; cerebellar/vestibular signs; peripheral neuropathy possible; hepatomegaly	Enzyme assay in leucocytes; cultured fibroblasts
	Mucopolysaccharidosis (MPS) VII	Progressive paraparesis	Urine metabolite screening a; DNA for related cats
	Mucolipidosis II (I-cell disease)	Dysmorphism; failure to thrive; delayed mineralization; skeletal abnormalities; retinal degeneration at 2.5 months of age	Inclusions in cultured fibroblasts; serum lysosomal enzyme assay <sup>a</sup>
Korat	GM <sub>2</sub> gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide urinalysis &b enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
Norwegian Forest Cat	Glycogenosis IV	Incoordination; exercise intolerance	DNA testing <sup>a</sup>
Persian	Mannosidosis	8 weeks at onset; connective tissue and skeletal malformation; possible peripheral nerve pathology	Oligosaccharide urinalysis a,b
Siamese	GM <sub>1</sub> gangliosidosis	Young animals show cerebellar signs; may have dwarfism and facial dysmorphism	Oligosaccharide urinalysis ab; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
	Niemann-Pick type A	Cerebellar/vestibular signs; depression; peripheral neuropathy	Enzyme assay in leucocytes; cultured fibroblast
	Mucopolysaccharidosis (MPS) VI	Dysmorphism; paraparesis	DNA testing a; urine metabolite screening ab
	Ceroid lipofuscinosis	Adult and juvenile forms; ataxia; seizures; progressive blindness (central ± retinal)	Skin biopsy to look for lipopigment

A1.3 Inborn errors of metabolism of the central nervous system in cats. <sup>a</sup> PennGenn Laboratories, University of Pennsylvania, Genetics Unit. <sup>b</sup> Comparative Neuromuscular Laboratory, University of California. <sup>c</sup> Jefferson Medical College, Department of Neurology, Philadelphia.

**Appendix 1** Neurological disorders associated with cat and dog breeds

Breed	Disease	Clinical signs (including age of onset where known)	Diagnosis
Akita	Glycogenosis (Type III)	Muscular weakness; hepatomegaly	Liver; muscle; nervous system pathology
American Bulldog	Neuronal ceroid lipofuscinosis	1–4 years; retinal blindness; mental deterioration; seizures; tremors; dysmetria	Pathology
Australian Cattle Dog	Ceroid lipofuscinosis	1 year; progressive visual loss and ataxia	Skin biopsy to look for lipopigment; brain pathology
Basset Hound	Lafora's disease	Myoclonic epilepsy	Muscle biopsy to look for intracytoplasmic PAS-positive inclusions
Beagle	GM, gangliosidosis	Young animals show cerebellar signs; may have dwarfism and facial dysmorphism	Oligosaccharide urinalysis a; enzyme assay in whole skin, cultured skin fibroblasts; liver; leucocytes
	Lafora's disease	Myoclonic epilepsy	Muscle biopsy to look for intracytoplasmic PAS-positive inclusions
* 46	Globoid cell leucodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis; cerebral signs later; may have peripheral neuropathy	DNA testing <sup>b</sup> ; peripheral nerve biopsy is suggestive of diagnosis; enzyme assay in leucocytes; cultured fibroblasts
Border Collie	Ceroid lipofuscinosis	Adult and juvenile forms; ataxia; seizures; progressive blindness (central ± retinal)	Skin biopsy to look for lipopigment
Boxer	Niemann-Pick type C	Ataxia; cerebellar/vestibular signs; peripheral neuropathy; possible hepatomegaly	Enzyme assay in leucocytes; cultured fibroblasts
Cairn Terrier	Globoid cell leucodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis; cerebral signs later; may have peripheral neuropathy	DNA testing <sup>b</sup> ; peripheral nerve biopsy is suggestive of diagnosis; enzyme assay in leucocytes; cultured fibroblasts
Chihuahua	Ceroid lipofuscinosis	Adult and juvenile forms; ataxia; seizures; progressive blindness (central ± retinal)	Skin biopsy to look for lipopigment
Clumber Spaniel	Pyruvate dehydrogenase deficiency (metabolic myopathy)	3 months; progressive exercise intolerance and collapse	Enzyme assays using cultured fibroblast; organi acid analysis <sup>a</sup>
Cross-breed dog	Mucopolysaccharidosis (MPS) VII	Pelvic limb weakness; joint laxity; atrioventricular valve incompetence seen in affected dogs	DNA testing a; urine metabolite screening a.c.
Dachshund	Lafora's disease	Myoclonic epilepsy	Muscle biopsy to look for intracytoplasmic PAS-positive inclusions
	Ceroid lipofuscinosis	Adult and juvenile forms; ataxia; seizures; progressive blindness (central ± retinal)	Skin biopsy to look for lipopigment
	Mucopolysaccharidosis IIIA	Adult onset; progressive spinocerebellar ataxia	Heparan sulphate urinary excretion; fibroblast and hepatic enzyme assay
English Setter	Ceroid lipofuscinosis	Adult and juvenile forms; ataxia; seizures; progressive blindness (central ± retinal)	Skin biopsy to look for lipopigment
English Springer	Fucosidosis	Adult onset cerebral signs (1-4 years)	DNA test for carrier or affected animal ad
Spaniel	GM <sub>1</sub> gangliosidosis	Young animals show cerebellar signs; may have dwarfism and facial dysmorphism	Oligosaccharide urinalysis ac; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
German Shepherd Dog	Glycogenosis (Type III)	Muscular weakness; hepatomegaly	Liver; muscle; nervous system pathology
German Shorthaired Pointer	GM₂ gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide urinalysis ac; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
Irish Setter	Globoid cell leucodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis; cerebral signs later; may have peripheral neuropathy	DNA testing <sup>b</sup> ; peripheral nerve biopsy is suggestive of diagnosis; enzyme assay in leucocytes; cultured fibroblasts
Japanese Spaniel	GM₂ gangliosidosis	Cerebellar/vestibular signs	Oligosaccharide urinalysis ac; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
Labrador Retriever	Mucopolysaccharidosis (MPS) II	Incoordination; exercise intolerance; visual deficits	Urine metabolite screening <sup>a</sup>

Inborn errors of metabolism of the central nervous system in dogs. <sup>a</sup> PennGenn Laboratories, University of Pennsylvania, Genetics Unit. <sup>b</sup> Jefferson Medical College, Department of Neurology, Philadelphia. <sup>c</sup> Comparative Neuromuscular Laboratory, University of California. <sup>d</sup> Animal Health Trust, Genetics Units, Newmarket. <sup>e</sup> VU University Medical Center, Amsterdam. <sup>f</sup> Further differentiation of L- versus D-isomer type requires submission of 2-hydroxyglutaric aciduria samples to a speciality laboratory for isomer isolation. PAS = periodic acid—Schiff (stain). (continues)

Breed	Disease	Clinical signs (including age of onset where known)	Diagnosis
Lapland Dog	Glycogenosis (Type II)	Muscle weakness; vomiting; megaoesophagus; cardiac and respiratory abnormalities	Liver; muscle; nervous system pathology; EMG abnormalities
Maltese Terrier	Malonic aciduria	Seizures; stupor	Urine organic acid screening a,c
Miniature Pinscher	Mucopolysaccharidosis (MPS) VI	Dysmorphism; paraparesis (spinal abnormalities)	DNA testing a; urine metabolite screening a,c
New Zealand Huntaway Dog	Mucopolysaccharidosis IIIA	1–2 years; progressive ataxia; hypermetria	Lysosomal enzyme assay
Old English Sheepdog	Cyłochrome c oxidase deficiency	3 months; exercise intolerance; generalized weakness	Pre- and post-exercise lactate and pyruvate; electromyography; muscle biopsy
Plotthound	Mucopolysaccharidosis (MPS) I	Dysmorphism; spinal abnormalities	Urine metabolite screening <sup>a</sup>
Poodle	Globoid cell leucodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis; cerebral signs later; may have peripheral neuropathy	DNA testing <sup>b</sup> ; peripheral nerve biopsy is suggestive of diagnosis; enzyme assay in leucocytes; cultured fibroblasts
	Neonatal encephalopathy	From birth; mentally dull; small; weak; ataxic tremors; extensor rigidity at 4–5 weeks	Exclusion diagnosis; urine organic acid measurement
Portuguese Water Dog	GM <sub>1</sub> gangliosidosis	Young animals show cerebellar signs; may have dwarfism and facial dysmorphism	Oligosaccharide urinalysis ac; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
Schipperke	Mucopolysaccharidosis (MPS) IIIB	3+ years; progressive cerebellar signs	Urine metabolite screening a.c; enzyme assay in cultured fibroblasts
Siberian Husky	GM <sub>1</sub> gangliosidosis	Young animals show cerebellar signs; may have dwarfism and facial dysmorphism	Oligosaccharide urinalysis a.c; enzyme assay in whole skin; cultured skin fibroblasts; liver; leucocytes
Silky Terrier	Glucocerebrosidosis (Gaucher disease)	6–8 months of age at onset ataxia; hypermetria; cerebellar signs	Enzyme assay (beta-glucosidase) in leucocytes
Staffordshire Bull Terrier	L-2-hydroxyglutaric aciduria	Ataxia; seizures; dementia; onset 4–10 months of age	Urine organic acid screening a,e,f
Sussex Spaniel	Pyruvate dehydrogenase deficiency (metabolic myopathy)	3 months; progressive exercise intolerance	Enzyme assays cultured fibroblast; organic acid analysis <sup>b</sup>
Tibetan Terrier	Ceroid lipofuscinosis	Adult and juvenile forms; ataxia; seizures; progressive blindness (central ± retinal)	Skin biopsy to look for lipopigment
West Highland White Terrier	Globoid cell leucodystrophy (Krabbe's disease)	Early cerebellar signs and ascending paralysis; cerebral signs later; may have peripheral neuropathy	DNA testing <sup>b</sup> ; peripheral nerve biopsy is suggestive of diagnosis; enzyme assay in leucocytes; cultured fibroblasts
Wire-haired	Mucopolysaccharidosis (MPS) III	Ataxia; intention tremor	Urine metabolite screening <sup>a</sup>
Dachshund	Lafora's disease	Myoclonic epilepsy	Muscle biopsy to look for intracytoplasmic PAS-positive inclusions

(continued) Inborn errors of metabolism of the central nervous system in dogs. <sup>a</sup> PennGenn Laboratories, University of Pennsylvania, Genetics Unit. <sup>b</sup> Jefferson Medical College, Department of Neurology, Philadelphia. <sup>c</sup> Comparative Neuromuscular Laboratory, University of California. <sup>d</sup> Animal Health Trust, Genetics Units, Newmarket. <sup>e</sup> VU University Medical Center, Amsterdam. <sup>f</sup> Further differentiation of L- *versus* p-isomer type requires submission of

VU University Medical Center, Amsterdam. Further differentiation of L- versus p-isomer type requires submission of 2-hydroxyglutaric aciduria samples to a speciality laboratory for isomer isolation. PAS = periodic acid-Schiff (stain).

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# **Appendix 2**

# **DAMNITY** classification of diseases

The 'mechanism' of disease responsible for a neurological disorder can be one of 10 broad categories; each category describes a multitude of specific diseases listed in the table below. Consideration of each of these mechanisms, based on patient signalment, presenting complaint, clinical history and the neurological examination, should take place following localization of the

neurological lesion(s). The ultimate aim is to develop a list of differential diagnoses for the patient.

Specific disorders are described in a chapters based on presenting problems. As a result, many disorders are relevant to more than one chapter. The numbers in square brackets refer to the chapter or chapters in which the disease is considered in greatest detail.

Mechanism of disease	Specific diseases
Degenerative	Calcinosis circumscripta [13, 14, 15]; canine cognitive dysfunction [8]; cerebellar cortical degeneration [12]; cervical stenotic myelopathy (Wobbler syndrome) [14]; degenerative myelopathy [15]; degenerative lumbosacral stenosis (LSS) [18]; dural ossification [13, 15]; feline encephalomyelopathy [12]; foraminal stenosis [16]; inherited neurodegenerative diseases [8]; intervertebral disc disease [13, 14, 15, 18]; Labrador Retriever myopathy and exercise-induced collapse [17]; lysosomal storage diseases [10, 12]; mucopolysaccharidosis [15]; muscular dystrophy [17]; myotonia [17]; neurodegenerative brain diseases [8, 12]; peripheral neuropathy [14]; spinal cord disease [14]; spinal synovial cysts [14, 15]; spondylosis deformans [13, 15]
Anomalous	Atlantoaxial instability [13, 14]; Chiari-like malformations [10, 13]; congenital abnormalities in eye position [9]; congenital deafness [11]; congenital vestibular disease [10]; dermoid sinus [14, 15]; dysmyelination/hypomyelination [12]; feline cerebellar hypoplasia [12]; hydrocephalus [8]; lissencephaly [9]; osteochondromatosis [14, 15]; scoliosis [13]; vertebral and spinal cord anomalies [13, 14, 15, 18]
Metabolic	Calcium abnormalities [7, 12]; diabetes mellitus [14]; endocrine neuropathies [14, 15]; hepatic encephalopathy [8]; hyperadrenocorticism [14, 17]; hypoglycaemia [8]; hypothyroidism [10, 14]; metabolic myopathies [17]; myxoedema coma [8]; potassium abnormalities [8]; sodium abnormalities [8]
Neoplastic	Brain tumours [8, 10]; chordomas [18]; choroid plexus tumours [8]; gliomas [8]; inner and middle ear tumours [10]; insulinoma [14]; lipomas [18]; lymphoma [16]; meningiomas [8]; nerve sheath tumours [11, 16]; paraneoplastic neuropathy [14]; pituitary tumours [8]; spinal lymphoma [15]; spinal neuroepithelioma [15]; vertebral body tumours [15]; vertebral plasma cell tumours [15]
Nutritional	Hypervitaminosis A [13]; thiamine deficiency [8, 10]
Inflammatory (immune- mediated and infectious)	Bacterial encephalitis [10]; canine distemper virus infection [10]; canine distemper viral myelitis [15]; chronic inflammatory demyelinating polyneuropathy [14]; cryptococcosis [10]; discospondylitis [13, 14]; empyema [13]; encephalitis [8, 10]; extraocular myositis [9]; feline encephalomyelitis [12]; feline infectious peritonitis, myelitis and meningitis [10, 15]; feline leukaemia virus-associated myelopathy [15]; feline spongiform encephalopathy [12]; ganglioradiculitis [14]; generalized tremor syndrome in dogs [12]; granulomatous meningoencephalomyelitis (GME) [10, 13]; infectious meningitis [13]; infectious polymyositis [17]; inflammatory myopthies [17]; inflammatory spinal cord diseases [15]; masticatory myositis [11]; meningitis [8]; meningoencephalitis [10]; meningoencephalomyelitis [14]; myasthenia gravis [17]; nasopharyngeal polyps [10]; necrotizing meningoencephalomyelitis [10]; neosporosis [10]; optic neuritis [9]; osteomyelitis [13]; otitis media/interna (OM/OI) [10] parasitic diseases [8]; plexus neuritis [16]; polioencephalomyelitis [12]; polyarthritis [13]; polymyositis [13]; polyradiculoneuritis [14]; presumed immune-mediated cerebellar granulprival degeneration in Coton de Tulear dogs [12]; protozoal myelitis [15]; protozoal neuritis [14]; spinal empyema [14, 15]; steroid-responsive meningitis—arteritis (SRMA) [13, 14]; tail abscessation [18]; toxoplasmosis [10]; vertebral physitis [15]
Idiopathic	Arachnoid cysts [10, 14, 15]; canine and feline dysautonomia [18]; disseminated idiopathic skeletal hyperostosis [15]; distal denervating disease [14]; feline hyperaesthesia syndrome [12]; Homer's syndrome [9]; hypertonicity in Cavalier King Charles Spaniels [17]; idiopathic epilepsy [7]; idiopathic facial paresis [11]; idiopathic vestibular disease [10]; Laforas disease [17]; laryngeal paralysis [11]; megaoesophagus [11]; narcolepsy–cataplexy [8]; reflex myoclonus [12, 17]; Scottie cramp [17]
Toxic	Antiepileptic drugs [7, 15]; botulism [14]; drug-induced toxic neuropathy [14]; ivermectin [8]; lead [8]; metronidazole [10]; organophosphate/carbamate [12, 17]; ototoxicity [10]; tetanus [14, 16]; tick paralysis [14]
Traumatic	Brachial plexus avulsion [16]; caudal lumbar trauma—lumbosacral trauma [16]; cervical vertebral fractures and luxations [14]; femoral nerve injury [16]; fractures and luxations of the caudal lumbar and sacral vertebrae [18]; fractures and luxations of the thoracolumbar spine [15]; hea trauma [10]; inner ear trauma [10]; lumbosacral plexus trauma [16]; middle ear trauma [10]; pelvic trauma [16]; peroneal and tibial nerve injury [16]; proximal sciatic nerve injury [16]; radial nerve injury [16]; sacral fractures [18]; sacrococcygeal fracture/luxation and tail avulsions [18]; spinal cord contusion [14]; thoracolumbar fractures and luxations [15]; traumatic disc herniation [14]
Vascular	Aortic thrombosis [15]; brachial thrombosis [16]; canine cerebrovascular accidents [8, 10, 12]; cerebrovascular disease [10]; coccygeal muscle injury [18]; feline ischaemic encephalopathy [8]; fibrocartilaginous embolism (FCE) [14, 15, 18]; spinal haemorrhage [14]

# **Appendix 3**

# **Conversion table for units**

	SI unit	Conversion factor	Conventional unit
Haematology		100	
Red blood cell count	1012/1	Cast of R. 1 - Charles	10 <sup>6</sup> / μl
Haemoglobin	g/I	0.1	g / dl
MCH	pg / cell	1	pg / cell
MCHC	g/I	0.1	g/dl
MCV	fl	1	μm³
Platelet count	10 <sup>9</sup> / I	1	10 <sup>3</sup> / μl
White blood cell count	10 <sup>9</sup> / I	Salar Salar Salar	10 <sup>3</sup> / μl
Biochemistry	er in the American	Salar salares	da e
Alanine aminotransferase	IU/I		IU/I
Albumin	g/I	0.1	g/dl
Alkaline phosphatase	IU/I	1	40 IU/I (6)
Aspartate aminotransferase	IU/I	1	IU/I
Bilirubin	μmol / l	0.0584	mg / dl
BUN	mmol / I	2.8	mg / dl
Calcium	mmol / I	4	mg / dl
Carbon dioxide (total)	mmol / I	1	mEq/I
Cholesterol	mmol / I	38.61	mg / dl
Chloride	mmol / I	1000 534	mEq/I
Cortisol	nmol / I	0.362	ng / ml
Creatine kinase	IU/I	1	IU/I
Creatinine	μmol / I	0.0113	mg / dl
Glucose	mmol / I	18.02	mg / dl
Insulin	pmol / I	0.1394	μIU / ml
Iron	μmol/l	5.587	μg / dl
Magnesium	mmol / I	2	mEq/I
Phosphorus	mmol / I	3.1	mg / dl
Potassium	mmol / I	1	mEq/I
Sodium	mmol / l	1	mEq/I
Total protein	g/I	0.1	g / dl
Thyroxine (T4) (free)	pmol / I	0.0775	ng / dl
Thyroxine (T4) (total)	nmol / I	0.0775	μg / dl
Tri-iodothyronine (T3)	nmol / l	65.1	ng / dl
Triglycerides	mmol/I	88.5	mg / dl
Serum drug levels			
Bromide	mmol/l	8	mg/dl
Phenobarbital	mmol/l	0.232	mg/l

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"A DRES SALAZAR"

# **BSAVA Manual of**

# **Canine and Feline Neurology**

# Third edition

Edited by Simon R. Platt and Natasha J. Olby

This new edition of the BSAVA Manual of Canine and Feline Neurology has been completely rewritten and restyled since the last edition was published in 1995. The changes reflect the rapid and extensive additions to this field of veterinary medicine that have taken place over the last 10 years.

The basic organization of the earlier editions is retained in this Manual.

The first section of the Manual discusses the essential requirements



for making a neurological diagnosis and includes: neurological examination; lesion localization and differential diagnosis; clinical pathology; electrophysiology; and neuroradiology. The neuroradiology chapter represents the greatest change, with more detail on the advanced imaging techniques, while retaining thorough descriptions of radiographic techniques. A new chapter on tissue biopsy is also included in this section.



The second section of the Manual focuses on different presenting problems. A number of chapters, including coma, stupor and behavioural change, neck and back pain, and tail, anal and bladder dysfunction, have been added since the previous edition due to the overwhelming increase in information now available on both new and previously described diseases. Each chapter in this section presents the diseases in a similar way, detailing clinical presentation, pathogenesis, diagnosis, treatment and prognosis.

The final section of the Manual contains completely new chapters devoted to therapeutics. The chapters include: emergency presentations (detailing spinal trauma, head injury and status epilepticus); anaesthesia, analgesia and supportive care; clinical pharmacology; radiotherapy; neurosurgery (indications and complications); and rehabilitation of the neurological patient.

The chapters throughout the Manual are accompanied by stunning specially commissioned full-colour illustrations.

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The neurological examination; Lesion localization and differential diagnosis; Clinical pathology; Electrophysiology; Neuroradiology; Tissue biopsy; Seizures; Coma, stupor and behavioural change; Disorders of eyes and vision; Head tilt and nystagmus; Neurological abnormalities of the head and face; Tremor and involuntary movements; Neck and back pain; Tetraparesis; Paraparesis; Monoparesis; Exercise intolerance, collapse and paroxysmal disorders; Tail, anal and bladder dysfunction; Neurological emergencies; Anaesthesia, analgesia and supportive care; Principles of neurosurgery; Drug therapy for diseases of the central nervous system; Radiation therapy of the nervous system; Nursing and rehabilitation of the neurological patient; Appendices; Index.

